19th Annual Meeting, American College of Chest Physicians
New York City, May 28 - 31, 1953

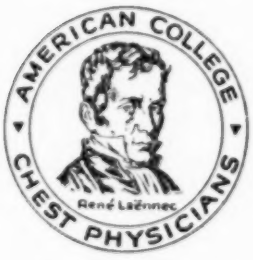
VOLUME XXIII NUMBER 1

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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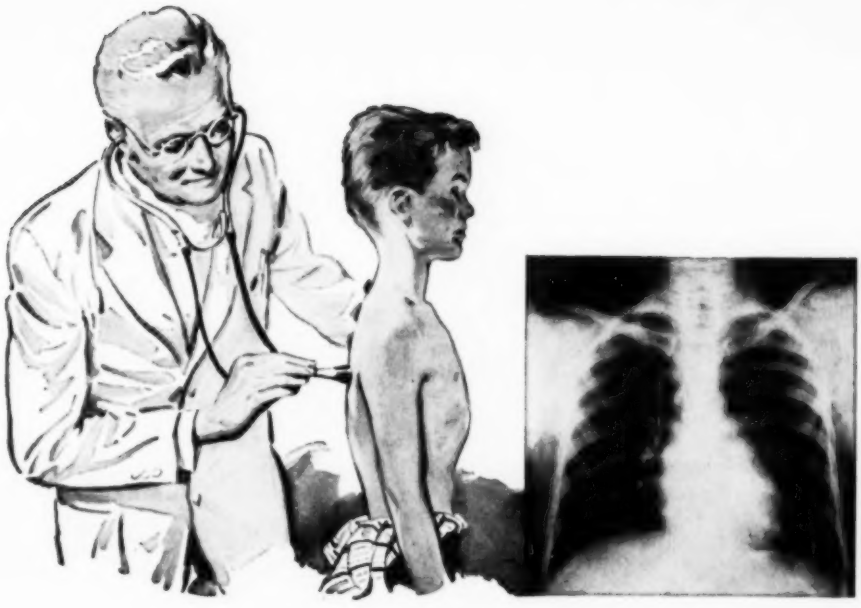

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DISEASES *of the* CHEST

OFFICIAL PUBLICATION

OF THE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
112 East Chestnut Street, Chicago 11, Illinois
MURRAY KORNFELD, *Managing Editor*

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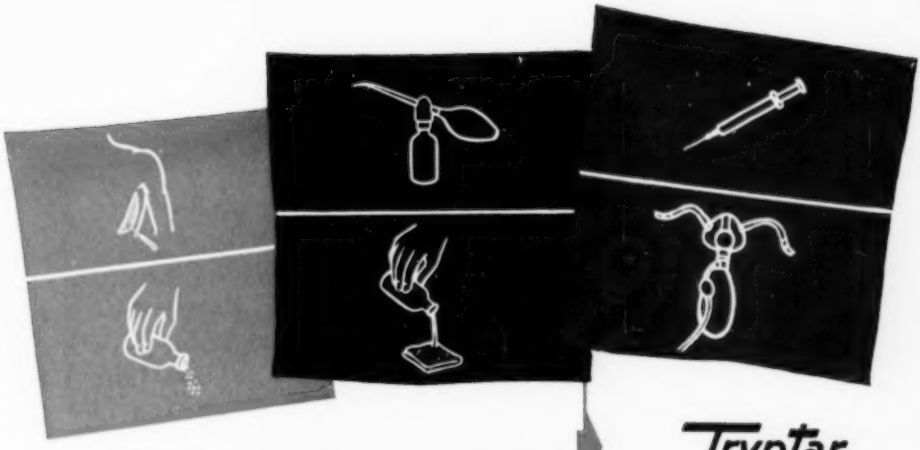

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First course of treatment: After sputum cultures were obtained, the patient was treated with procaine penicillin, intramuscularly, 150,000 units daily for 5 days and streptomycin 0.5 Gm. t.i.d. for 4 days. In addition, he was given penicillin inhalations for 6 days. Postural drainage was employed throughout the treatment.

Response: The amount of expectorate decreased but slightly.

On December 4, the patient was transferred to the Department of Thoracic Surgery of a larger hospital, for operation. Bronchoscopic examination revealed marked bronchiectasis in all segments of the left lower lobe. The upper lobe, including the lingula, showed no abnormality. The sputum volume was now 600 cc. per day.

Second course of treatment: In the hope of reducing the sputum volume before operation, the patient was given 'Neo-Penil', intramuscularly, 1 million units the first day, 1 million units b.i.d. the second day, and 1 million units t.i.d. thereafter. Postural drainage was reinstituted.

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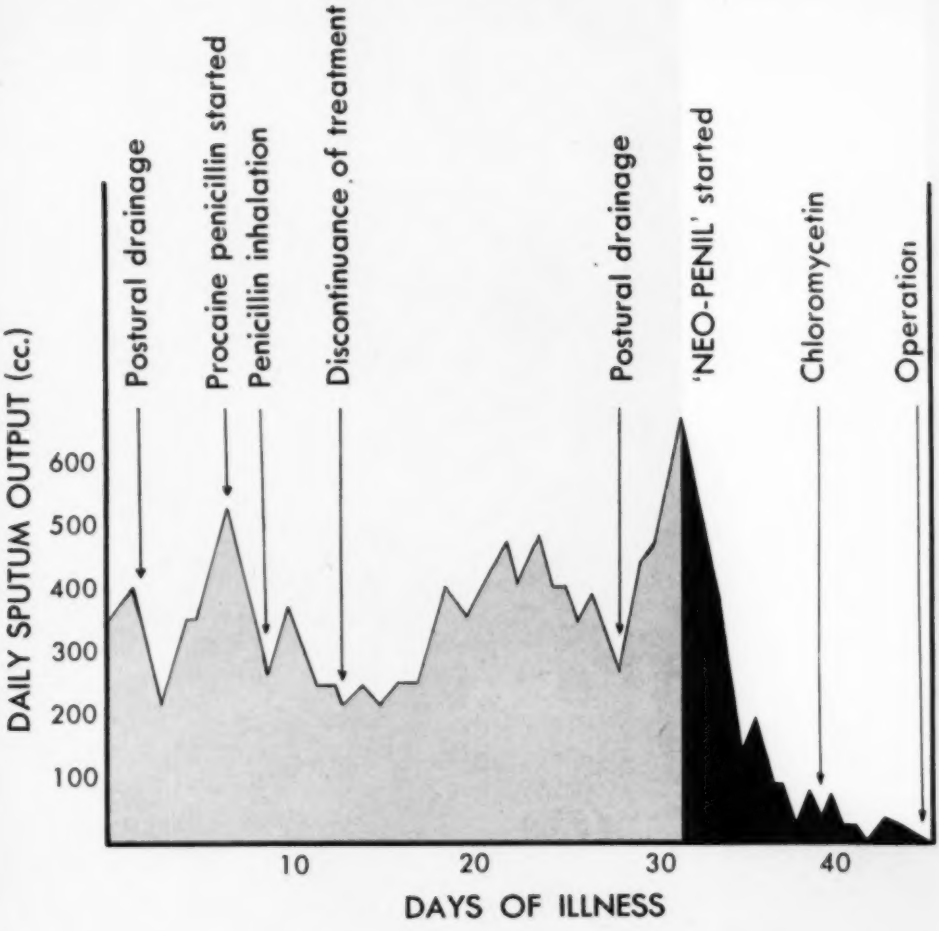

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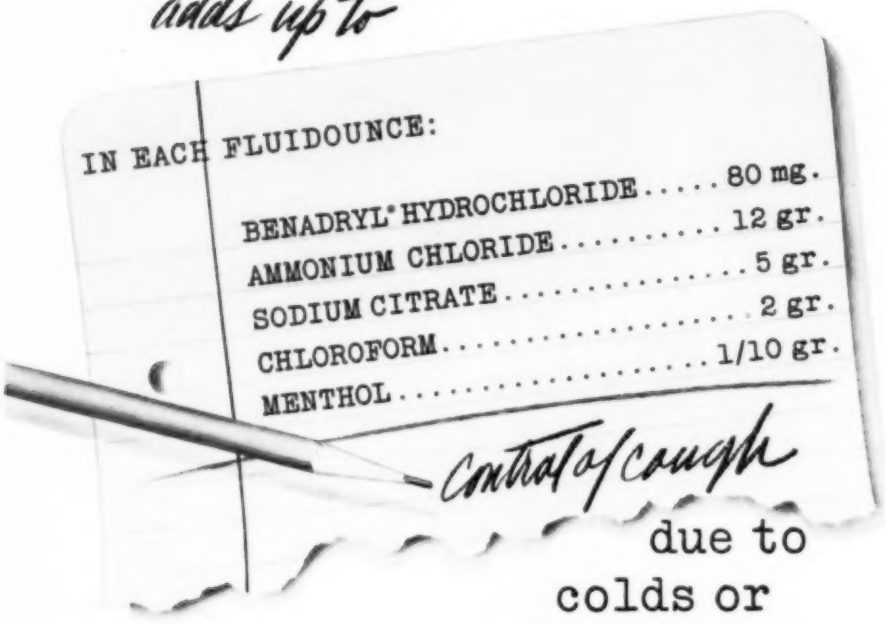

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1. Ansbro, F. P., and others. Anesthesiology 13:306, 1952. 2. Jason, A. H., and Shattel, H. E. Postoperative Pain Control, presented before the Section on Anesthesiology of the American Medical Association, Chicago, Ill., June 10, 1952. 3. Deaton, W. R., Jr., and Bradshaw, H. H. Am. Surgeon 18:616, 1952. 4. Puderbach, W. J., and others. Journal Lancet 72:203, 1952. 5. Tucker, C. C. J. Kansas M. Soc. 53:230, 1952. 6. Gross, J. M., and others. New York State J. Med. 52:1413 (June 1) 1952. 7. Penn, S. E. Arch. Otolaryng. 56:59, 1952. 8. Cappe, B. E., and Pallin, I. M. Am. Pract. & Digest Treat. 3:739, 1952.

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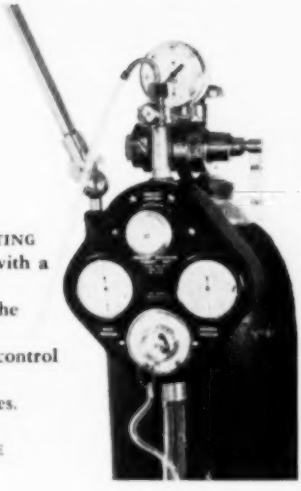

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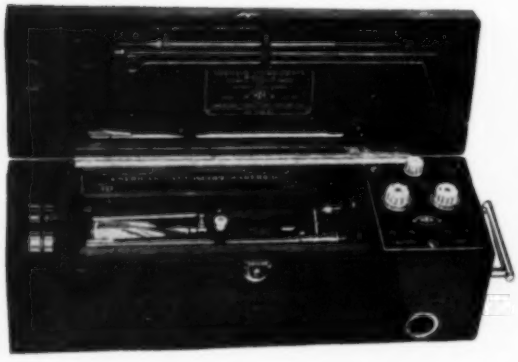

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DISEASES *of the* CHEST

VOLUME XXIII JANUARY 1953 NUMBER 1

Isoniazid and Its Isopropyl Derivative in the Therapy of Tuberculosis in Humans: Comparative Therapeutic and Toxicologic Properties*

EDWARD H. ROBITZEK, M.D., F.C.C.P., IRVING J. SELIKOFF, M.D., F.C.C.P., ERICH MAMLOK, M.D. and ANNA TENDLAU, M.D.
Staten Island, New York

Early experiences with the hydrazide of isonicotinic acid and its glucosyl and isopropyl derivatives in the therapy of human tuberculosis at Sea View Hospital have been reported.[1-3] Significant beneficial clinical and laboratory chemotherapeutic effects were noted in a majority of the 92 patients studied. Of this number, 82 were treated for from five to 15 weeks with the isopropyl derivative while 10 were treated with the parent compound (isoniazid) for four weeks. No comparison was ventured concerning the therapeutic efficacy of the two drugs since the groups under treatment were dissimilar in number and duration of therapy. The individual groups were documented as such, but the overall results were given generally as indicating the chemotherapeutic activity of the hydrazides of isonicotinic acid.

Additional experiences have now been obtained. The original group of 92 patients has continued under therapy and observation and an additional 83 have been brought under treatment, principally with isoniazid. All of these patients have now been treated for from nine to 34 weeks. Although additional patients have subsequently been brought under treatment, they are not included in this report since shorter periods of observation are now considered to be less suitable for evaluation.

Iproniazid (Marsilid)

The criteria utilized in the selection of patients for study in this series have been previously detailed.[1-3] Briefly, all had caseous pneumonic tuberculosis with cavities and sputum positive for tubercle bacilli. All had had one or more of the standard forms of therapy including rest, pneumothorax, surgery, streptomycin,pneumoperitoneum, etc. When accepted for study it was judged, in each case, that no other standard form of therapy could reasonably be expected to rapidly alter the progressive or stationary course

*From the Medical Service, Sea View Hospital, George G. Ornstein, M.D., Medical Director.
Isoniazid (Rimifon).
Isopropyl Derivative of Isonicotinic Acid (Marsilid).
Drugs kindly supplied by the Hoffmann-La Roche Co. of Nutley, New Jersey.

of the disease. Data with regard to composition of the total series is summarized in Table I.

Marsilid was administered after meals in three daily divided doses. It was uninterrupted. All therapy was oral, in tablet form. Other treatments

TABLE I: Analysis of Case Material.

	Marsilid	Rimifon	Hydrazide Plus Streptomycin
Total Cases	101	65	9
Sex:			
Males	65	38	5
Females	36	27	4
Race			
White	45	26	4
Negro	46	33	2
Puerto Rican	10	5	2
Yellow	0	1	1
Average Age (Years)	40.5	41.6	38.7
Previous Duration of Disease:			
6 months	11	4	1
7-12 months	20	4	1
13-24 months	25	22	2
Over 24 months	45	35	5
Previous Therapy:			
Streptomycin	78	52	1
Courses of streptomycin	126	106	1
PAS	83	45	4
Tibione	0	2	0
Pneumothorax	36	21	7
Diasone	0	2	1
Pneumoperitoneum	21	16	1
Surgical Excision or Collapse	7	6	0
Extrapulmonary Tuberculosis:			
Larynx (23)	14	9	0
Otitis (4)	3	1	0
Tongue (2)	1	1	0
G.I. (2)	2	0	0
Lymph Node (2)	1	1	0
Empyema (12)	4	7	1
Sinuses, etc. (8)	1	7	0
Others (5)	2	3	0

were discontinued except for unilateral pneumothorax in a few cases wherein it had established control over one lung without beneficially affecting the progressive uncontrolled, active disease in the contralateral lung.

The standard dosage employed has been 4 mg./K. of body weight, although brief studies were undertaken utilizing other dosages for short periods. Thus, 1, 2, 10 and 15 mgs./K. were utilized for brief periods but were not found desirable. The dosages below 4 mg./K. failed to yield comparable therapeutic effects while dosages at 10 and 15 mg./K. did not yield significantly superior therapeutic effects to compensate for the increasing incidence of toxic manifestations; they were therefore discarded.

Results of Therapy

Systemic: Our initial observations with regard to the rapid and significant effect of Marsilid on the systemic manifestations of the tuberculous process have been confirmed. This has been true in almost all cases and in each there was an abrupt reversal of the previous course. Defervescence usually occurred promptly and often was complete by the end of the second week. Occasionally it was precipitous. It was delayed by the presence of mixed-infection empyema or non-tuberculous infection. This defervescence has been permanent in all but a few cases. Appetite usually returned promptly. Corresponding weight increases were sometimes noted almost immediately upon the institution of therapy but occasionally did not begin until the third or fourth week. The overall weight gain has averaged almost two pounds per person per week and has tended to continue until normal or slightly above-normal levels were reached. In some instances increases of 60 or more pounds occurred. Gains were more rapid and of greater degree in those patients initiating therapy at the more marked sub-normal weight levels. It was slower and rarely did not occur in those patients who began therapy at or above normal weight. General toxicity abated rapidly and

TABLE II: Effect of Hydrazide Therapy on Toxicity of Active Tuberculosis.

	Marsilid (101)		Rimifon (65)		Hydrazide Plus Streptomycin (9)	
	Before Therapy	After Therapy	Before Therapy	After Therapy	Before Therapy	After Therapy
Temperature:						
Normal	38	96	27	57	3	9
Subfebrile (100°)	43	2	28	5	6	0
Febrile (101°-105°)	20	3	10	3	0	0
General Toxicity:						
None	26	96	25	51	5	9
+	28	2	17	13	3	0
++	25	3	17	1	1	0
+++	12	0	3	0	0	0
++++	10	0	3	0	0	0

return of strength and energy were usually noted by the second week. As with temperature, the salutory effects on toxicity have been maintained during continuation of therapy (in some cases over seven months) with five exceptions (Table II). Concommitant with the effect on the systemic manifestations of tuberculosis has been marked reduction and in some cases abolition of cough and expectoration (Table III).

Roentgenographic Changes

Among the 101 patients, serial roentgenograms showed significant x-ray improvement in 59 (58.4 per cent). In 9 (8.9 per cent) progression of the disease, usually of minor extent, was noted. In 33 no significant roentgenographic change was observed. Roentgenographic improvement was relatively slow in appearing and was not noted in significant numbers of cases until three to five months of treatment had been completed. Possibly this may have been due to the extensive nature of the pathology. Roentgenographic improvement was evidenced by clearcut clearing of exudate or sharp diminution in cavity size or actual closure. There were 25 cavity closures, 19 reductions in cavity size and in 38 instances there was clearing of exudate. Almost all cavity closures have been confirmed by tomographic studies.

Effect on Sputum Bacteriology

All patients had sputum positive for acid-fast bacilli before institution of therapy. Conversion of sputum has occurred on smear concentrate, gastric concentrate and sputum culture in 26 (25.7 per cent). In addition, 25 (24.7 per cent) have shown marked reduction in bacillary counts showing only an occasional positive sputum. A number of patients continue to have highly positive sputa. We have occasionally noted "negative" sputa with persistence of cavitation on roentgenogram. Many of these reconverted to positivity at a later date. Thus residual open cavities have tended to signify pending sputum relapse and after six months of therapy there is close correlation between cavity closure and sputum negativity, confirmed by culture.

Extra-Pulmonary Tuberculosis

A wide variety of extra-pulmonary tuberculous lesions were seen. Fourteen with tuberculous laryngitis were treated with uniform success; healing was

TABLE III: Effect of Hydrazide Therapy on Cough and Expectoration.

	Marsilid (101)		Rimifon (65)		Hydrazide Plus Streptomycin (9)	
	Before Therapy	After Therapy	Before Therapy	After Therapy	Before Therapy	After Therapy
None	7	57	4	33	1	8
+	17	34	19	27	0	1
++	41	10	24	5	5	0
+++	26	0	14	0	3	0
++++	10	0	4	0	0	0

complete in approximately two months although symptomatic improvement was invariably noted in two to seven days. Satisfactory results were obtained in the treatment of tuberculous glossitis, empyema sinus tracts, gastro-intestinal tuberculosis, tuberculous wound infections, tuberculous otitis media and tuberculous lymphadenitis. Favorable experiences with renal and orthopedic tuberculosis have been reported.[4,5] Consistently favorable therapeutic effects on tuberculosis of the excretory tracts, sinuses and wounds have been noteworthy.

Drug Toxicity

At the therapeutic dose of 4 mg./K. there has been but minimal significant toxicity.[6] No parenchymatous damage to liver, kidney or hemopoetic system has been detected in the group under treatment. There has been no evidence of agranulocytosis. No allergic reactions have occurred to this date. There has been no gastro-intestinal intolerance.

With some regularity moderate diminutions of hemoglobin averaging two to three grams have been noted. The anemia is self-limited in most cases and has not been aggravated by sickle-cell anemia, present in three instances. Temporary interruption of therapy in one case of an elderly man seemed advisable. Recovery of normal hemoglobin levels occurred promptly and without adjuvant therapy.

Central nervous system and autonomic nervous system side effects are, however, common. There appears to be wide individual variation in this regard in many patients, especially in the younger and middle-aged groups, where often there are no or, at most, minimal side effects of this nature. In the older age groups (over 50 years) these side effects occur more regularly and with greater intensity. The effects most commonly encountered are vasomotor vertigo, especially on rising, constipation, involuntary muscle twitching, hyperreflexia, delay in micturition, mild euphoria and, occasionally, headaches. These side effects have usually subsided by the fourth week of therapy although hyperreflexia tends to persist. Similar side effects are often noted upon abrupt drug discontinuance and appear to formulate a definite pattern of withdrawal symptoms. Patients most commonly complain of excessive dreaming, excitation, restlessness and headache. They are often noticably irritable.

Such toxic side effects are apparently aggravated by adrenergic drugs, large doses of intravenous barbiturates, demerol and anti-histamines. They may become more serious with the administration of general anesthesia and may be excessive in patients with previous psychotic or unstable personalities. Novocaine has been used in large quantities without ill effect. Marsilid appears to augment a pre-existing convulsive state. *These side effects are much more intense at high dosage levels and thereby constitute a limiting factor in dosage regimens of Marsilid therapy.*

Mortality

There have been seven deaths among the 101 patients under treatment. One had hemorrhaged before the onset of therapy, continued to bleed

despite therapy and died in several weeks of hemorrhagic suffocation. This was confirmed on post-mortem examination. A second with extensive pulmonary disease developed bronchopneumonia in his remaining functioning pulmonary tissue and died. This occurred while under therapy and we feel that it was probably a tuberculous spread and is considered as such. The post-mortem material is currently under study and will be reported independently. A third had a destroyed left lung and a contralateral upper lobe cavity which closed under hydrazide therapy. Left excisional surgery was recommended but not accepted by the patient. Subsequently, she suffered a fatal hemoptysis. Post-mortem examination confirmed death due to hemoptysis and also revealed generalized amyloidosis. A fourth patient died of pulmonary emphysema with pulmonary insufficiency. It was present before therapy and intensified progressively until exitus. Autopsy confirmed the clinical findings. Another, aged 70, died of coronary infarction. A sixth, who had previously suffered from convulsions, was treated with 15 mg./K. He suffered another convlusion from which he failed to recover. Post-mortem examination with careful neuro-pathological investigation failed to reveal abnormalities. We consider that the high dosage used for treatment may have contributed to this fatal outcome. The seventh, with extensive pulmonary tuberculosis, died suddenly. Post-mortem study revealed that, in addition to the pulmonary tuberculosis, bronchial carcinoma was present. Death was due to shock following perforation of the tumor into the esophagus and mediastinum.

Parenthetically, it should be noted that autopsies were obtained in six of these seven cases. No significant parenchymatous organ damage was found.

Isoniazid (Rimifon)

The same criteria with regard to selection of patients for therapy that were utilized in the previous group were applied here. All were caseous-pneumonic, cavitary and sputum positive. However, with increasing experience and confidence, cases with somewhat less extensive disease were selected for therapy. This is not reflected in the rigid and inadequately descriptive classifications currently utilized. In this relationship the later series even included a small number of cases with unilateral disease who might conceivably have been suitable for trial of collapse therapy. Data concerning the composition of this group are presented in Table I.

Rimifon, as with Marsilid, was administered orally, uninterrupted and in divided doses. Dosage regimens employed were principally 4 mg./K. and 8 mg./K. Smaller dosages, instituted earlier, were abandoned because of inadequate and retarded therapeutic effect. Experiences with dosages higher than 4 to 8 mg./K. are of more recent date and are referred to below.

Results of Therapy

Systemic: The systemic effect on the tuberculous process with isoniazid therapy is qualitatively similar to that observed under treatment with its isopropyl derivative. However, *in the dosage ranges employed*, these bene-

ficial systemic effects have not appeared with the same regularity nor to the same degree as with the isopropyl derivative. Thus, defervescence is often slower and has occasionally failed of completion. In some instances, on the other hand, it approximated that observed with Marsilid. Similarly, symptomatic improvement with regard to general toxicity, strength, energy and appetite, was common but not invariable. Weight increases began more slowly and averaged half the amounts elicited by Marsilid therapy. Individual variations were more common. In many instances, the improvement resembled that seen with Marsilid. Cough and expectoration followed the same general pattern, occasionally abolished, often reduced, rarely uneffected.

Roentgenographic Changes

Favorable x-ray changes have been statistically comparable to those observed with Marsilid therapy. Cavity closure occurred nine times among 64 cases. Significant diminution in cavity size was seen 16 times; clearing of exudate occurred 25 times. Spread of the disease occurred once and was minor. One cavity increased in size. These x-ray findings have been, on the whole, observed in a shorter period of time than those in the group treated with Marsilid. Whether this is due to inherent characteristics of the drugs or to differences in the severity of the disease in the two groups, is difficult to state with certainty at the present time.

Effect on Sputum Bacteriology

All but three patients were positive at the institution of therapy. These three were treated for lymphadenitis, persistent sinus without active pulmonary disease and peri-anal ulcer respectively. Sixteen (25.8 per cent) are at present negative on smear concentrate, gastric concentrate and culture. Eighteen (28 per cent) show significant reductions in sputum bacillary concentrations being only occasionally positive for acid-fast bacilli. Sputum conversions have correlated well with the roentgenographic changes.

Extrapulmonary Tuberculosis

Results in treatment of extrapulmonary tuberculosis are similar to those observed under Marsilid therapy. Indeed, the major portion of our experiences with extrapulmonary tuberculosis has been with Rimifon and has been uniformly satisfactory. In addition to the varieties tabulated above, therapy has been employed in the post-operative management of cavernostomy and in tuberculosis of the skin.

Toxicity

No significant toxic side effect has been observed in parenchymatous organs or hemopoetic system. Abnormalities of the cephalin flocculation tests and the albumin/globulin ratios were slight and transitory. Central nervous system and autonomic nervous system side effects are qualitatively similar to those observed with Marsilid but are much less frequently ob-

served and in considerably lesser degree at the dosages employed. Nevertheless, significant side effects involving the central nervous system, reminiscent of those seen with high dosages of Marsilid, have been rarely observed even at the 4 to 8 mg./K. levels.

Mortality—None.

Comparison of Marsilid and Rimifon

Repeated clinical observations, reflected only in part in the above statistics, indicate that there are both similarities and differences in the activity of the two drugs under consideration.

With regard to the alleviation of systemic aspects of tuberculosis, Marsilid enjoys a clear superiority over Rimifon in the dosages employed. Our data indicate that weight gain with Marsilid is prompt, almost invariable and sustained. It correlates with improvement in appetite, loss of general toxicity, defervescence and reduction of cough and expectoration. The pattern of this response is usually established within two weeks. Rimifon, in the dosages employed, is less predictable, often delayed and occasionally incapable of overcoming temperature elevation. Total weight gain is rarely as spectacular and residual symptoms are occasionally seen. Although it is readily apparent that the sicker, more toxic patients experienced the more dramatic improvement and although the Marsilid group contained a higher percentage of such toxic patients, the Rimifon group also contained representative numbers and their response did not approximate that which had been commonly observed within the Marsilid group. Thus, in combatting the systemic ravages of progressive caseous pneumonic tuberculosis, Marsilid, dose for dose, enjoys a clear superiority.

Roentgenographic Changes

Preliminary statements[1-3] pointed out that favorable x-ray changes during the first five to 15 weeks of therapy failed to match the obvious clinical results. It is noteworthy therefore, that tabulations made with more prolonged therapy now indicate significant x-ray improvement in 60 per cent of cases. This occurs with both Marsilid and Rimifon. The earlier appearance of favorable x-ray change with Rimifon is possibly more apparent than real, since, as noted, the inadequacies of classification cannot differentiate the degree of advancement among far-advanced cases. It is our opinion that roentgenographic changes have been approximately equal in the two groups studied.

Effect on Sputum Bacteriology

It is of interest that the percentages of sputum conversion and reduction in the overall series at this time coincide with those reported at 15 weeks. At that time, however, there was a high percentage of negative sputa in cases with open cavities. Many of these have shown subsequent positive sputa but the current negativity, confirmed by culture, correlates closely with cavity closure. Therefore, comparison statements which apply to x-ray generally apply to sputa and the apparent statistical equality of

the two drugs must be examined with reference to the excessive advancement of the disease in the Marsilid treated patients.

Drug Toxicity

The almost complete absence of toxicity in Rimifon-treated patients and the liberal incidence of side reactions among those under Marsilid therapy establishes clear-cut superiority for the former drug in this regard. It is fortunate that such reactions are usually self-limited and reversible, but they do constitute a source of annoyance to the patient and call for closer supervision of the physician. Hemoglobin reductions with Marsilid are appreciable but not serious and respond promptly to simple drug discontinuance or other appropriate measures. No increase in bleeding tendencies have been noted with either drug.

Mortality

Deaths have been limited to the Marsilid group and have been tabulated above. It is probable that Marsilid therapy augmented the convulsive tendencies in patient E. B. We are of the opinion that at this stage of the investigation, a history of convulsions or personality disturbance contraindicates the use of this agent. The remaining deaths are of the varieties seen among severely ill tuberculous patients and attest more to the degree of advancement in the group chosen than to variations in the drugs.

Blood Levels

In summary, then, it may be stated that *dose for dose*, Marsilid appears to be more active, albeit more toxic. This is at variance with the studies *in vitro* and in animals where the reverse is true[8] but may possibly be explained by blood level studies which clearly show that utilizing equimolar dosages, Marsilid promptly reaches two to three times the blood levels attained by Rimifon and after 12 hours, with the latter virtually exhausted, satisfactory levels of Marsilid are still maintained.[11]

Extra-pulmonary Tuberculosis

Each drug has demonstrated effectiveness in the treatment of tuberculous laryngitis, otitis, glossitis, adenitis and enteritis. Ulcerations, fistulae and sinus tracts have closed or been markedly benefited by each agent. Since no two lesions are identical, statistical comparisons are not possible. However, it is our impression that closures under Marsilid therapy are more rapid, and in a few instances of failure with Rimifon, success was obtained with Marsilid.[9]

Dosage of Rimifon

It will be noted that three cases have been under therapy with 4 mg./K. of Rimifon and 33 with 8 mg./K. The statistical evaluations fail to reveal major differences in response over the period of investigation. It is our impression that beneficial effects are seen more promptly at the higher dosage levels. Most important is the failure to observe any increase in toxicity in the higher dosage group over the lower. We have also studied

therapy with dosages of 20 mg./K. of body weight and five cases were so treated for over two weeks. Drowsiness was noted and one personality disturbance has forced us to abandon this level. We do not recommend this dosage at this time.

Dosage Regimens

All early studies were conducted with drug administration three times daily in divided doses. Six patients under Rimifon and five under Marsilid have been given their entire daily dosage in a single morning administration. We have found that this method is effectual in the treatment of various types of tuberculous lesions. But an obviously slower response in some instances as well as incomplete defervescence dictated reversion to multiple dosage. We are currently investigating every four hours dosage and preliminary impressions, unsupported by statistical data, suggest some superiority with this regimen. Blood level studies after single doses, multiple doses and at various periods thereafter, indicate a peak level at about one and one-half hours post ingestion with gradual reduction over the subsequent 12 hours. A practical and satisfactory dosage regimen is divided dosage, after meals and on retiring. Obviously, at dosages employed, frequent divided dosages are more desirable with Rimifon than with Marsilid because of the more satisfactory persistence of blood levels in the latter instance.

Nine patients under treatment with both drugs in combination with streptomycin (5 Marsilid, 4 Rimifon) are under study. The results are entirely satisfactory with each but the series is insufficient for statistical evaluation.

Bacterial Drug Resistence

The difficulties encountered with the development of bacterial resistence during streptomycin therapy of tuberculosis, pose the problem of bacterial drug resistence in the evaluation of any new chemotherapeutic agent. This was recognized during our early studies with the hydrazine derivatives of isonicotinic acid.[1-3] In our continuing current investigations, studies of bacterial drug resistence are being conducted on sputa of all patients under treatment.

Preliminary data are available on the first reported results in this group,* and are reproduced in Table IV. Only one patient, E. L., shows significant "resistence" to hydrazines. This patient, with far-advanced bilateral cavitary tuberculosis, was treated for 105 days with Marsilid, initially at a level of 10 mg./K. for six weeks and since then at 4 mg./K. Bacterial cultures showed the lowest growth inhibiting concentration to be 12.5 mcg./ml., which is above the sensitivity levels of normal controls and somewhat above the blood levels possible on the dosage levels utilized. All other bacterial cultures in this group show drug sensitivity well within therapeutic blood levels and within the approximate sensitivity range of un-

*These studies have been made in cooperation with Dr. R. J. Schnitzer and Dr. E. Grunberg of the Chemotherapy Laboratories, Hoffmann-La Roche Co., Nutley, N. J. Technique: Dilution Method, Subculture Technique, Dubos Medium.

treated controls. Since these include cases treated for from 42 to 277 days, with an average of 112 days, it would indicate that bacterial resistence is apparently late in developing and of lesser degree than with streptomycin.

It is possible that the single resistent strain noted in this group may not have developed this resistence but may have been so resistent *de novo*, before treatment. It is known that such inherently insensitive strains may occasionally occur.

The correlation of the possible development of drug resistence with

TABLE IV: Sensitivity Tests in Vitro with Strains of M. Tuberculosis from Sputa of Untreated Patients and Patients Treated with Hydrazines.

Name of Patient	Treatment			Lowest Growth Inhibiting Concentration	
	Drug	Dose (mgm/K.)	Duration (Days)	Rimifon (mcg/ml.)	Streptomycin (mcg/ml.)
S.S.	Untreated	—	—	0.006	0.0195
G.J.	Untreated	—	—	0.025	10.0
S.H.	Untreated	—	—	0.025	0.625
V.E.	Untreated	—	—	0.098	5.0
M.F.	Untreated	—	—	0.025	0.0097
L.P.	Untreated	—	—	0.049	0.098
L.R.	Untreated	—	—	0.025	0.625
T.B.	Untreated	—	—	0.049	0.156
T.T.	Rimifon	8	42	0.098	0.3125
C.P.	Rimifon	8	56	0.78	0.312
E.A.	Rimifon	4	94	0.049	0.15
R.M.	Rimifon	4	99	0.39	10.0
M.B.	Rimifon	2	64	0.049	0.078
M.D.	Marsilid	4	60	0.05	—
J.W.	Marsilid	4	60	0.09	—
R.M.	Marsilid	4	66	0.39	2.5
M.K.	Marsilid	4	94	0.049	2.5
E.L.	Marsilid	5	105	12.5	10.0
R.P.	Marsilid	4	124	0.195	10.0
H.M.	Marsilid	4	145	1.56	1.25
M.N.	Marsilid	4	150	0.19	—
E.O.	Marsilid	4	169	0.098	0.31
H.C.	Marsilid	4	277	0.098	10.0
L.D.	Marsilid	4	118	0.78	—
H.C.	Marsilid	4	169	0.78	0.156
R.D.	Marsilid	4	124	0.098	0.0098
G.S.	Marsilid	4	120	0.098	0.312

clinical refractoriness to therapy is difficult at present. The patient E. L. discussed above was noted to have a resistent strain in a culture taken March 15, 1952. Yet review of her clinical course since that date indicates continued clinical and roentgenographic improvement. Moreover, we have recently temporarily interrupted hydrazine therapy in a large group of patients who had been under treatment for five to seven months. Two patients showed clinical relapse, with recurrence of toxicity and high fever. (One was L. D., in Table IV, whose sputum culture before interruption of therapy showed bacteria with normal drug sensitivity). Both of these patients were restarted on Marsilid. Both showed an immediate clinical response, with rapid defervescence and loss of toxicity, cough and expectoration, indicating absence of drug resistence. Moreover, in our total series under treatment, we have not observed those complete returns to pre-therapy toxicity, fever, cough, expectoration and clinical and roentgenographic deterioration which we have customarily observed with streptomycin, when bacterial resistence to that antibiotic has developed.

Bacterial drug resistence studies are of importance and both extensive and intensive investigations should be encouraged. Data obtained therein, when correlated with therapeutic studies, will be of assistance in determining optimum dosage schedules, duration of therapy, advantages of combined therapy, etc. It is hoped that such data will be rapidly forthcoming, with establishment of methods for the optimum utilization of the hydrazine derivatives of isonicotinic acid, and avoiding the many years that were required for determination of desireable schedules for utilization of streptomycin.

Discussion

It has been emphasized throughout this paper that dose for dose, Marsilid exerts a more rapid and profound therapeutic effect in the treatment of several varieties of tuberculosis. Nevertheless, *in vitro* studies indicate manifold superiority of Rimifon over Marsilid.[8] For Marsilid, in our hands, 4 mg./K. represents the tentative optimum dosage since it combines therapeutic efficacy of a high order with an adequate margin of safety. It is apparent that the optimum dosage and dosage regimen for Rimifon, on the other hand, has not been determined and a proper comparison between the two drugs is not possible until such has been found. Incomplete data suggest that higher dosages can well be tolerated and there is reason to believe that better therapeutic results may be anticipated at higher dosage levels. Initial caution with Rimifon was predicated on animal studies which predicted chronic toxicity.[10] This has not been detected in several thousands of liver function, blood, urine and other studies over eight months. This presumably is a reflection of a curious animal specificity which tends to limit dogs to 15 or 20 mg./K., while allowing rats a tolerance of 1400 mg./K. Monkeys also show a much better tolerance than dogs.[12]

Conversely, minimal dosages have been established. Some beneficial therapeutic effect is seen between 0.75 and 2 mg./K. of Rimifon. However, such response is unpredictable, meagre and often delayed. Such dosages in our hands have been unsatisfactory.

Marsilid at 4 mg./K. and Rimifon at 4 and 8 mg./K. in divided doses have yielded therapeutic results clearly superior to those observed in this hospital with streptomycin or streptomycin combined with PAS for equivalent durations of therapy. Our own data with regard to treatment using minimally effective doses of Rimifon, such as 2 mg./K., are inadequate to allow for comparison with streptomycin-PAS. Since these doses are inadequate they may be anticipated to produce results not significantly superior to those yielded by streptomycin-PAS treatment. Certainly Marsilid in our hands has demonstrated effectiveness over systemic toxicity in a manner unlike any previous drug with which we have worked.

SUMMARY

1) One hundred and one patients under iproniazid (Marsilid) at 4 mg./K., 65 under isoniazid (Rimifon) at 4 and 8 mg./K., and nine under combined streptomycin and iproniazid or isoniazid therapy for from two to seven months have been compared with respect to effect on acute toxicity, x-ray, sputum, extrapulmonary tuberculosis and drug toxicity.

2) *Dose for dose*, the systemic effects of tuberculosis are more promptly and completely controlled by iproniazid than by isoniazid.

3) X-ray changes and sputum bacteriology show approximately equal benefit.

4) Drug toxicity is encountered more frequently and more intensely with iproniazid than with isoniazid.

5) Beneficial effects with each drug are seen in the treatment of various extrapulmonary entities.

6) The combination of streptomycin with either isoniazid or iproniazid appears to demonstrate some superiority to either drug alone on the basis of a short term study of nine cases.

7) Clinical resistence to hydrazide therapy has not been impressive.

8) The first 17 patients, under treatment for from 42 to 277 days with an average of 112 days, continued to show in vitro sensitivity with one exception.

9) Optimum dosage and dosage regimen for isoniazid has not been determined but is believed to be in excess of 8 mgs. per kilo in divided doses.

RESUMEN

1) Se han comparado ciento un enfermos tratados con iproniazida (Marsilid) a razón de 4 mg. por kilo de peso, sesenta y cinco enfermos con isoniazida (Rimifon) a la dosis de 4 y 8 mg. por kilo de peso y nueve enfermos con tratamiento combinado de estreptomicina ya sea con iproniazida o con isoniazida, enfermos que han sido observados de dos a siete meses a fin de determinar su efecto sobre la toxicidad aguda de la enfermedad, sobre el aspecto radiológico, sobre los esputos, sobre la tuberculosis extrapulmonar y para precisar la toxicidad de la droga.

2) A dosis semejantes los efectos generales de la tuberculosis son más pronta y completamente dominados por la iproniazida que por la isoniazida.

3) El efecto sobre la apariencia radiológica y sobre la bacteriología del esputo es parentemente igual con ambas drogas.

4) La toxicidad de la droga se encuentra más frecuente e intensa con la iproniazida que con la isoniazida.

5) Se observan efectos benéficos con ambas drogas en varias afecciones extrapulmonares.

6) Basándose solo en los nueve casos observados, la combinación de estreptomicina con isoniazida o de iproniazida, parece demostrar alguna superioridad sobre cualquiera de las drogas mencionadas, sola.

7) La resistencia clínica al tratamiento con hidracida no es notable.

8) En los 17 primeros enfermos bajo tratamiento de 42 a 277 días con un término medio de observación de 112 días, se ha continua observando sensibilidad a la droga in vitro, con excepción de uno.

9) La dosificación óptima y el régimen para la isoniazida no se han determinado pero se cree que ha de ser más de 8 mg. por kilo en dosis fraccionadas.

RESUME

1) Les auteurs rapportent les observations de cent-un malades, traités par l'iproniazide (dérivé isopropyle) sous forme de "Marsilid" à la dose de 4 milligrammes par kilogramme et les observations de soixante cinq malades traités par l'isoniazide sous forme de "Rimifon" à la dose de 4 à 8 milligrammes par kilogramme, ainsi que celles de neuf malades traités par l'association de streptomycine avec l'iproniazide ou l'isoniazide; le traitement à été poursuivi de deux à sept mois. Il a été jugé en fonction de son action sur l'intoxication du malade, l'aspect radiologique de ses lésions, ses crachats, les localisations extra-pulmonaires, et la toxicité possible de la drogue.

2) A dose égale, l'action sur l'état général est plus rapide et plus complète pour l'iproniazide que pour l'isoniazide.

3) Au point de vue radiologique et de l'examen bactériologique des crachats, l'action est approximativement la même.

4) Les effets toxiques du produit sont plus fréquents et plus intenses avec l'iproniazide qu'avec l'isoniazide.

5) Les effets favorables de chacune de ces drogues ont été notés sur les différentes tuberculoses extra-pulmonaires.

6) La combinaison de streptomycine avec l'isoniazide ou l'iproniazide semble donner la preuve d'une certaine supériorité par rapport à la drogue seule. Mais ceci n'est basé que sur une étude très limitée, ne comportant que neuf cas.

7) Du point de vue clinique, l'établissement d'une résistance à la thérapeutique par les dérivés de l'hydrazide n'a pas été bien évidente.

8) A part une exception, les auteurs ont constaté que les premiers dix-sept malades qui ont été traités pendant 42 à 277 jours avec une moyenne de 112 jours, continuent à être sensibles *in vitro* à ce produit.

9) La posologie de l'isoniazide n'a pas été déterminée avec précision, mais semble dépasser 8 milligrammes par kilogramme en doses fractionnées.

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Clinical Experiences with Isonicotinic Acid Hydrazide in Tuberculosis†

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Isonicotinic acid hydrazide (Rimifon††) has within recent months received widespread acclaim as an antituberculosis drug. This compound was first synthesized by Fox and subsequent investigations have indicated that this agent is bacteriostatic and bacteriocidal against M. tuberculosis in vitro; seems to have a tuberculocidal effect in vivo against mice; and a dramatic beneficial effect in guinea pigs, rabbits[1,3] and monkeys.[4]

Preliminary clinical studies of the drug by Robitzek, Selikoff, and Ornstein indicated that isonicotinic acid hydrazide and its derivatives exert a profound and important therapeutic effect in human tuberculosis. The mortally ill patients which these authors studied responded with therapeutic benefits never seen with any of the chemotherapeutic or antibiotic agents previously utilized by them.[5]

These investigations prompted us to study a series of patients critically ill with tuberculosis and to evaluate the effectiveness and toxic potentialities of one of these newer preparations.

Material and Method:

Twenty male cases were studied: 12 with bilateral far advanced caseous-pneumonic tuberculosis; four with bilateral moderately advanced caseous-pneumonic tuberculosis; one with miliary tuberculosis and tuberculous pericarditis; one with tuberculosis of the spine "Pott's Disease" with abscess formation and pleural effusion; one with tuberculous peritonitis; and one with suspicious caseous-pneumonic tuberculosis.

Before institution of therapy each patient had a complete physical examination, chest roentgenogram, complete blood count, erythrocyte sedimentation rate (Westergreen), blood urea nitrogen determination, total serum protein and albumin-globulin level, cephalin cholesterol flocculation test, prothrombin time (one-stage Link-Shapiro modification of the Quick method), urinalysis, and a baseline weight. These procedures were carried out at weekly intervals for the first six weeks and then performed bimonthly with the exception of the urinalysis, chest roentgenograms and weights which have been repeated at weekly intervals. A daily 24 hour sputum was collected, weighed and sent to the laboratory for a Ziehl-Nielsen stain and Gaffky determination. During the latter part of this

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††Rimifon was supplied through the courtesy of Dr. Leo Pirk, of the Hoffman-LaRoche Company, Nutley, New Jersey.

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study the sputum was cultured in order to determine viability and sensitivity of tubercle bacilli. The results of these studies will be reported at a later date. A 3,600 calorie balanced "routine hospital" diet with supplemental feedings as desired was administered to all patients. Tomographs were not performed. The rectal temperatures were recorded in the majority of cases twice daily and in the remainder at four hour intervals.

Dosage: The initial dose was 1 mgm. per kg. of body weight for three days followed by 2 mg. per kg. of body weight for three days then increased to 4 mg. per kg. of body weight. The latter dosage was maintained for approximately seven weeks. At present most patients are receiving 5 mg. per kg. of body weight. The drug was administered by mouth three times a day after meals. No other therapeuic protcedures were carried out on the patients in this series.

Results

The results are divided into systemic and local responses.

Systemic Response:

Appetite—was greatly improved in 15 cases, somewhat improved in three, and not improved in two. The most marked improvement of appetite was observed in 12 patients in the first two to three weeks of treatment, but this improvement lessened by the seventh week. This decline of appetite was attributed in some instances to the type of food served. A certain degree of psychic loss of appetite was apparent. The poorest appetite was observed in general in the most critically ill patients. Only one patient developed a "tremendous" appetite.

Energy and Sense of Well Being: It is extremely difficult to evaluate these features inasmuch as the patients knew they were a select group receiving a special drug which had been much publicized. However, generally the group seemed to feel better within a week to 10 days after institution of therapy. Those patients with marked toxicity and clouding of the sensorium became more rational and less apathetic. These findings appeared to parallel the lowering of the temperature levels.

Night Sweats: Eleven noted definite decrease in severity of night sweats; one observed an increase in severity; and eight did not complain of night sweats as a prominent symptom.

Temperature: Sixteen were febrile for varying periods before onset of therapy. The temperature in this group subsided slowly and it was four to five weeks before normal levels were obtained (See Figure 1). No precipitous drops were observed. Frequent low grade spikes from 100.5 to 101 degrees F. were noted in several cases which apparently had returned to normal temperatures. Four patients who were afebrile before institution of treatment have remained afebrile up until the 15th week despite the presence of positive sputa at varying times in the course of the study.

Weight: Seventeen gained an average of 9.6 pounds in the average of 12.3 weeks of therapy. These weight gains have become apparent in the third and fourth week of treatment. Three lost an average of 6.4 pounds

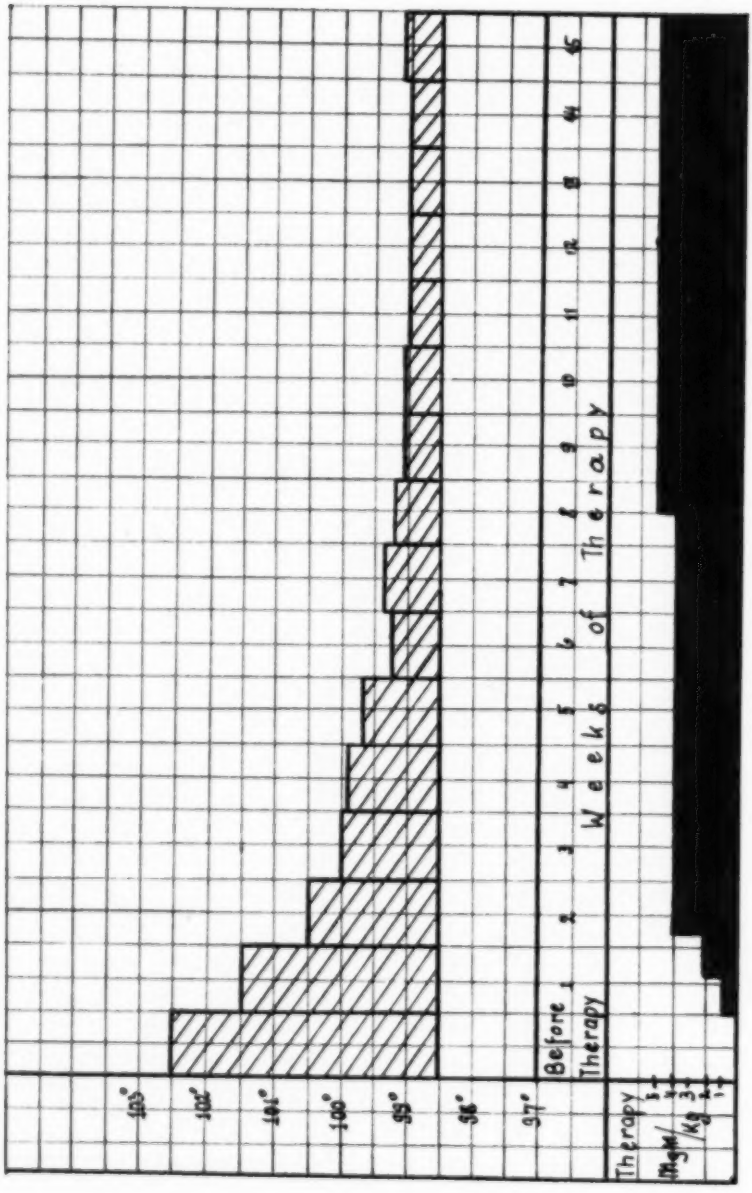

FIGURE 1: Average Temperature Response.
Sixteen febrile cases treated with isonicotinic acid hydrazide.

in the average of 8.2 weeks of therapy. Abnormal accumulations of body fluid were observed in this series in two cases but no effort was made to remove this fluid by mechanical means or diuretic agents (see Table I).

Response of Local Lesions:

Cough and Expectoration: Between the sixth and tenth weeks the cough had completely disappeared in three; become greatly improved in 12; moderately improved in one; not improved in one; and more severe in three. The daily 24 hour sputum collection showed no change of sputum weight with persistent copious amounts in 16 and a decrease of sputum weight in only four.

Sputum: Four patients had previously had streptomycin and PAS with negative sputa at the onset of therapy with isonicotinic acid hydrazide. Three of them developed positive sputa during therapy and have persistent positives in the 15th week ranging from Gaffky one to three. The fourth patient with tuberculous pericarditis and miliary tuberculosis had had two full courses of streptomycin in the past two years. Sputa were persistently negative during this period. After four, nine and 10 weeks of treatment with rimifon the first positive sputa were obtained. One patient who had previously had streptomycin and PAS with persistent positive sputa developed negative sputum four days after institution of rimifon, but subsequently developed positive sputa in the seventh and 15th week. Eleven with repeated positive sputa who had had no previous form of treatment before institution of rimifon therapy still had positive sputa in the 11th and 15th week of treatment. The Gaffky count in this group ranged from one to five with a mean of one to two. One patient with the most dramatic clearing of chest film had one positive sputum on admission and persistent negatives throughout the 14th week; it is doubtful whether this patient actually had tuberculosis since clearing had begun on a short course of penicillin before rimifon had been instituted. One with a dramatic clearing of chest sinuses who had had positive sputa while

TABLE I

AVERAGE WEIGHT GAIN AND LOSS AFTER THERAPY

(Duration of therapy 5 to 15 weeks)

Total Patients: 20	*No. of Patients*
Weight gain 0 to 10 pounds	11
Weight gain 11 to 20 pounds	5
Weight gain 20 to 25 pounds	1
Weight loss ½ to 12 pounds	3
Average weight gain	9.6 lbs.
Average duration of therapy	12.3 weeks
Average weight gain	6.4 lbs.
Average duration of therapy	8.2 weeks

on streptomycin and PAS also showed persistent negative sputa in the fifth week of treatment; however, he voluntarily discontinued medication and sputa became positive in the eighth week. The remaining patients had negative sputa but tubercle bacilli were found at other sites.

Chest Sinuses: The most dramatic response was observed in two patients with draining chest sinuses. One had a persistent sinus six months after pneumonectomy without evidence of healing and after a nine week course of streptomycin (42 gm. total) and PAS. After the first week of treatment with rimifon the sinus drained less and began to close. By the end of the second week abundant granulation tissue was observed and drainage ceased. However, this patient voluntarily discontinued medication and the sinus broke down with profuse drainage three weeks later. A similar course was observed in the second patient who had Pott's Disease of the spine with numerous healed and one large draining sinus over the sternum from which M. tuberculosis was cultured prior to treatment. This sinus had persisted for one year with profuse drainage. By the second week of treatment with rimifon the drainage stopped, good healing was noted and the sinus has

TABLE II: EFFECT OF THERAPY (5 to 15 weeks) ON ROENTGENOGRAPHIC APPEARANCE OF LESIONS

Type of Lesion	Weeks of Treatment	NUMBER OF PATIENTS		
		Greatly Improved	Some Improvement (Minimal Diminution Exudate)	No Improvement
Bilateral Far Advanced Caseous-Pneumonic Tuberculosis	5	-	-	1
	6	-	-	1
	10	-	-	3
	11	-	-	2
	12	-	1	-
	15	-	-	4
Bilateral Moderately Advanced Caseous-Pneumonic Tuberculosis	15	-	3	1
Tuberculosis Pericarditis with Miliary Tuberculosis	11	-	1	-
Suspected Tuberculosis (Probably Lobar Pneumonia)	14	1	-	-
Pulmonary Tuberculosis Tuberculous Peritonitis	9	-	-	1
Tuberculosis of Spine with Abscess Formation, Pleural Effusion and Draining Chest Sinus	7	-	-	1

remained closed up until the present (seven weeks). However, in the sixth week of treatment the first positive sputum was found.

Laryngeal Tuberculosis: One with combined far advanced pulmonary tuberculosis and tuberculosis of the larynx showed moderate improvement after nine weeks of treatment with rimifon.

Roentgenograms: Among 12 critically ill patients with bilateral far advanced caseous-pneumonic tuberculosis 11 showed no improvement in either amount of exudate or diminution in cavity size in from five to 15 weeks of treatment. In one, improvement was observed by the 12th week as evidenced by diminution of exudation. Among four patients with bilateral moderately advanced caseous-pneumonic tuberculosis under treatment for 15 weeks three showed minimal diminution of exudation. One with miliary tuberculosis and tuberculous pericarditis showed a diminution of the cardiac shadow by the eighth week and some clearing of the lung fields by the 10th week. One with a single positive sputum and a massive lobar involvement showed complete clearing. However, this patient had had penicillin before rimifon therapy was instituted and in all likelihood did not have pulmonary tuberculosis.

The remainder of the group were not improved from a roentgenographic standpoint (see Table II).

Toxicity and Side Reactions: No serious or untoward side reactions were encountered in this study necessitating discontinuance of the drug. Table III illustrates the side reactions observed. The majority of these occurred

TABLE III

Side Reactions	*No. of Cases*
Dizziness	7
Ataxia	2
Muscular Tremor	5
Hyperreflexia	7
Tinnitus	2
"Spots before eyes"	4
Headache	3
Vasomotor Instability (flushing)	3
Postural Hypotension	1
Nausea	4
Vomiting	3
Constipation	7
Loss of libido	1
Urinary Incontinance	1
Delay in initiation of micturition	1
Pruritis	11
Pustular Eruption of Skin	2

during the first two weeks of therapy; e.g., dizziness, muscular tremor (especially twitching of the eyelids), spots before the eyes, flushing and nausea. Constipation and pruritis was complained of throughout the entire course. When the dose was increased to 5 mg. per kg. of body weight, dizziness, nausea and vomiting was reported by three patients for 24 hours and then disappeared spontaneously without reduction of drug dosage. One Negro male complained of a marked reduction in libido and inability to maintain erection during sexual intercourse while under treatment.

Laboratory Studies

The prothrombin time was not influenced by the course of treatment. The total serum protein and its albumin-globulin constituents were not altered. One patient had a reversed A/G ratio prior to therapy and developed a 4+ cephalin flocculation reaction in the second week which has persisted into the 14th week. The cephalin flocculation determination showed a 1+ to 2+ reaction in seven cases before institution of treatment. Of these, six persisted with an occasional 1+ to 2+ and one described above as 4+ persisted throughout the course of treatment. Six cases with a negative reaction prior to treatment developed a 1+ to 3+ response during the course of treatment. The remainder of the group showed no changes.

The erythrocyte sedimentation rate was lowered to normal or near normal in six patients in from three to 13 weeks. The remainder of the group showed no change.

The repeated urine examinations showed no abnormalities which could be attributed to the drug when compared to pre-treatment controls.

The hemogram was not significantly altered except for eosinophilia ranging from five to 15 per cent observed in seven cases. The hemoglobin content was increased from 0.5 to 2.0 gm. and the red blood cells from 200,000 to 1,300,000 per cu. mm. in 12 cases and reduced slightly in three. The remainder showed no change.

Discussion

This preliminary study indicates that isonicotinic acid hydrazide influences primarily the systemic manifestations and to a much lesser extent the local lesions encountered in patients suffering from advanced tuberculosis. Our results although paralleling those of others[5,6] in several respects do not corroborate the marked dramatic beneficial effects previously reported. Improvement in appetite was noted in 90 per cent of our cases; however, in only one did a "tremendous" appetite develop. Eighty five per cent of this group gained an average of 9.6 pounds and 15 per cent lost an average of 6.4 pounds. The greatest weight gain of 25 pounds was observed in a patient who apparently did not have tuberculosis. This would indicate that the drug may have a stimulative metabolic effect causing weight gain in severely ill, emaciated patients and not necessarily a specific effect limited to tuberculosis. This is in contrast to the chronic feeding experiments in rats, where evidence for a "growth stimulant action" was not observed.[7] This factor is probably one of the most valuable assets of the

drug, inasmuch as patients under treatment with PAS frequently develop severe anorexia and subsequently impaired caloric intake with resultant weight loss. In general energy and sense of well being in the group increased, night sweats decreased in severity in 55 per cent of treated patients. The temperature response was in most instances similar to that observed in patients treated with streptomycin and PAS and took an average of four to five weeks before normal levels were obtained.

Whether this temperature response was due to a non-specific antipyretic effect of the drug, to the concomittant bed rest, or to the supposed bacteriostatic effect of the drug, is at the present time a matter of speculation even though the drug had no antipyretic effect in rabbits.[7] Further pharmacological studies on the temperature regulating centers in animals and man would appear indicated. On the whole the response of local lesions was not impressive. Although the cough had improved in 13 and completely disappeared in three the daily 24 hour sputum collection showed a decrease in sputum weight in only four. This is in variance with the observations of Selikoff and Robitzek who found that patients who had previously reported expectorations of 32 to 40 ounces of sputum per day, expectorated minor fractions of their original output during treatment.[6]

The definite value of any antituberculous preparation depends on its ability to eradicate the etiological agent and to cause regression of the roentgenographic lesion. This study shows that in only one doubtful case of pulmonary tuberculosis did conversion of a single positive sputum occur. Twenty per cent of cases who had previously had negative sputa after therapy with streptomycin and PAS developed positive sputa during treatment with rimifon. Fifty-five per cent of this group who had had no previous treatment and positive sputa initially still had positive sputa in the 11th and 15th week of therapy with rimifon. Although too small to be statistically significant, some of the findings of this series are in marked contrast to those of others.[5,6]

Although bacterial sensitivity studies to date have not been performed by us our clinical observations indicate that either bacterial resistance developed in this group or that the drug had deminished bacteriostatic or bacteriocidal qualities in humans. A recent report indicated that bacterial resistance developed in three of six patients after seven weeks of treatment and in one the first indication of increased resistance was apparent in 26 days. These observers also noted an initial fall in Gaffky count of these three patients followed by a rise at a time corresponding closely to the onset of increased bacillary resistance.[8] We have also observed sporadic rises in the tubercle bacillus count as late as the 10th and 15th week of treatment after initial drops of the tubercle bacillus count in the early part of our study in two patients.

Our preliminary observations further reveal that dramatic roentgen changes as evidenced by clearing of exudation and diminution or closure of single or multiple cavities did not appear during the period of treatment. In only five patients (25 per cent) was some (minimal) improvement observed as evidenced by diminution of exudate, one of these five with

tuberculous pericarditis and miliary tuberculosis showed a decrease of the cardiac shadow. However, these patients all have persistently positive sputa and the one with tuberculous pericarditis has a progressive downhill course clinically. These results are not as impressive as those reported by other investigators[6] and only time and further controlled observations can evaluate these variations.

One of the most impressive beneficial effects of the drug was observed in the rapid healing of draining sinuses. Similar preliminary observations have been reported by Bosworth, Wright and Fielding[9] utilizing the drug marsilid (1-isonicotinyl-2-isopropylhydrazine) in the treatment of tuberculous orthopedic lesions. We have also noted diminution of pain in several patients not included in this study, with bone tuberculosis.

Numerous side reactions of the drug are noted which may be due to a central stimulative effect or to imbalances occurring in the autonomic nervous system. The reported pharmacological investigations of the exact mechanism of these side effects in experimental animals are at present inconclusive.[7] The potential dangers of these drugs as shown in animal experiments, are indicated by a reduction in hemoglobin and hypochromic anemia as well as pathological changes in the reticulo-endothelial system in dogs,[7] renal damage in guinea pigs,[3] subacute toxicity in rats as evidenced by slight hepatic damage, and chronic administration in dogs resulting in fatty degeneration of the liver and jaundice.[10]

To the present time no serious toxic reactions have been observed in humans.[11]

Our study indicates that this drug may have a hepato-toxic effect in man as evidenced by the development of one to three plus response to the cephalin flocculation test in six patients who had a negative reaction prior to treatment. One patient who before treatment had a 1+ developed a persistent 4+ reaction. However, it is extremely difficult to evaluate this single abnormality since the hepato-cellular damage in these patients may be a manifestation of the general toxicity observed in tuberculosis.

No toxic manifestations relating to the hematopoietic system was noted although moderate eosinophilia occurred.

Conclusions

This study indicates that isonicotinic acid hydrazide does exert an antituberculous effect in humans; however this effect primarily combats the systemic toxicity and to a much lesser extent the local lesions observed in tuberculosis.

In a comparable group of patients treated for a similar period of time with streptomycin and PAS, the roentgenographic lesions showed more regression than was observed in this study. It was decided therefore to continue both forms of therapy. We now have six patients with far advanced tuberculosis receiving a combination of streptomycin and rimifon; and two moribund patients with tuberculous meningitis and peritonitis respectively with hematogenous spread are receiving streptomycin, PAS and rimifon for six to seven weeks. The appetite in these patients was

extremely poor prior to treatment and at present is excellent despite large doses of PAS. The temperature in the patient with tuberculous peritonitis decreased within eight days by lysis to normal levels. The temperature of the patient with meningitis became normal in four weeks and although the patient developed severe bilateral optic atrophy with total blindness the remaining neurological signs have receded. Both patients are markedly improved.

Inasmuch as these drug combinations have been used for a relatively short time no valid conclusion can be reached at present. However, the possibility exists that these drugs in combination may act in a synergistic manner and prove superior to any single preparation or previous combinations.

It is our opinion that in the present flux of our knowledge these newer preparations should be limited to institutional use and not be dispensed indiscriminately. Much more time and further investigations are needed before an accurate appraisal of isonicotinic acid hydrazide and its derivatives can be made.

SUMMARY

1) Twenty patients with tuberculosis have been treated for five to 15 weeks with isonicotinic acid hydrazide, and no other therapeutic measures.

2) The systemic manifestations of tuberculosis such as appetite, energy, night sweats, temperature, and weight appeared to be favorably influenced by the drug. The cough was decreased in the majority but 24 hours expectoration was lessened in only four. Sputum conversion occurred in only one instance; the remainder of the group has persistently positive sputa despite continued therapy. The possibility of development of bacterial resistance as evidenced by late rise in the Gaffky count in two patients is emphasized. Serial roentgenograms showed minimal diminution of exudation in only five cases, but positive sputa still persisted in these patients.

3) The toxicity and side reactions of the drug are described and suggestive evidence of a hepato-toxic effect in humans is discussed.

4) The possibility of synergism between isonicotinic acid hydrazide, streptomycin and PAS is stressed and preliminary favorable observations are presented.

Note: The Authors would like to express their thanks to Miss Ann Griffin, Charge Nurse of the Tuberculosis Ward, whose help facilitated this study.

RESUMEN

1) Veinte enfermos han sido tratados, por padecer tuberculosis, con hidracida del ácido isonicotínico durante 5 a 15 semanas sin agregar otra medida terapéutica.

2) Las manifestaciones generales de la tuberculosis tales como la falta de apetito, la temperatura, el peso, los sudores nocturnos y la astenia parecieron ser influenciados favorablemente. La tos disminuyó en la mayoría pero el volumen de la expectoración en 24 horas disminuyó solamente en 4 casos. La conversión de los esputos ocurrió solo en un caso; el resto del

grupo conservó sus esputos positivos a pesar de la terapia continuada. Se llama la atención sobre la posibilidad de aparición de resistencia por la elevación tardía del Gaffky en dos enfermos. La roentgenografía en serie mostro una disminución mínima de la exudación, solo en cinco casos pero en éstos persisten los esputos positivos.

3) La toxicidad y los efectos colaterales de la droga se describen y se discute la sugestiva evidencia de un efecto tóxico sobre el hígado en los seres humanos.

4) La posibilidad de efecto sinérgico entre la estreptomicina, el PAS y el acido isonicotínico se subraya y se presentan observaciones preliminares favorables.

RESUME

1) Les auteurs ont traité vingt malades atteints de tuberculose pendant une période de 5 à 15 semaines, avec l'hydrazide d'acide isonicotinique, sans autre thérapeutique associée.

2) Les troubles généraux dûs à la tuberculose semblent favorablement influencés par le produit. Il procure de l'appétit, de la force physique, fait disparaitre les sueurs nocturnes, baisser la température et augmenter le poids. La toux diminue chez la majorité des malades, mais l'expectoration mesurée sur 24 heures ne s'est montrée diminuée dans son volume que dans quatre cas. Il n'y eut qu'un cas où l'expectoration ne contint plus de bacilles de Koch; tous les autres continuent à renfermer des bacilles de Goch malgré un traitement prolongé. Les auteurs insistent sur la possibilité d'un développement de la résistance bactérienne, ainsi qu'il fut constaté chez deux malades. Les radiographies pratiquées en série ne montrèrent une diminution des lésions que dans cinq cas, et encore a-t-elle été minime. Chez ces malades toutefois, l'éxpectoration resta positive.

3) Les réactions d'accompagnement de ce traitement et sa toxicité sont l'objet d'une étude dans laquelle les auteurs discutent la possibilité d'un effet hépato-toxique chez l'homme.

4) Les auteurs insistent sur la possibilité de l'action synergique de l'association de l'hydrazide d'acide isonicotinique, avec la streptomycine et le PAS et en présentent des observations préliminaires favorables.

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Effects of Isonicotinic Acid Hydrazide in Mentally Ill Patients*

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Although the field of toxicity of isonicotinic acid hydrazide had been explored in experimental animals[1,5] prior to the first reports of its being employed as a therapeutic agent against tuberculosis in man,[2,3] and toxicity studies in humans had also been carried out,[4] there still remained an appeal for additional work to sustain the belief that this compound administered in low dosage over prolonged periods was not likely to produce harmful effects upon vital body structures. This report is based upon such an investigational study designed primarily to determine toxic effects of isonicotinic acid hydrazide as related to the liver, kidney and blood forming organs. In addition to exploring toxic manifestations, patients were observed for other side effects incident to administration of the drug, as well as for changes in their tuberculosis status.

Subjects to whom the medication was administered were tuberculous mentally ill patients in a state hospital for mental disease and were selected entirely on the basis of their pulmonary tuberculosis status without regard for their mental condition or diagnosis. Fifty such patients were originally included in the series and one patient suffering from a superimposed severe genitourinary tuberculosis was added. This last patient expired after 18 days of treatment as a result of renal failure and two of the original cases were discontinued after a few days trial because they were so uncooperative that it was considered hazardous to the patient to attempt to continue administration. The remaining 48 patients were carried on through the course for a period of 90 days. The daily dosages of drug was established on the basis of weight. Initially, 2 milligrams of drug per kilo of body weight per day was given and this dosage maintained for 10 days. The dosage was then increased to 4 milligrams per kilo per day at which level it was continued for the remaining days of the study; 200 milligrams per day being the minimal amount given to any one patient.

In preparing for study, a general clinical work-up on each patient was carried out with special attention to the following clinical and laboratory procedures:

1) Record of weight at the time treatment was started.
2) Five-day temperature check at 8 A.M. and 4 P.M.

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The pyricidin (isonicotinic acid hydrazide) used in this study was kindly provided by Nepera Chemical Company, Inc., Yonkers, New York.

3) Chest x-ray film studies.
4) A 24-hour urine concentration test for kidney function.
5) Bromsulphalein tests for liver function.
6) Complete blood, including red blood count, white blood count, differential count, hemoglobin determination and sedmindation rate.
7) A series of three gastric lavages for culture.

After classification of patient's disease according to the 1950 Diagnostic Standards of the National Tuberculosis Association, it was found that there were 26 patients with far advanced disease, 20 with moderately advanced disease and two diagnosed as minimal tuberculosis. All patients were known to be active cases as evidenced by clinical findings and/or the presence of tubercle bacilli in their gastric lavage specimens. Patients in this group ranged in age from 23 to 76 years. The distribution of cases by age and degree of pulmonary involvement is demonstrated in Table I. It is interesting to note that the greater number of these cases had old chronic tuberculosis with average durations of known disease ranging from 2.6 to 9.0 years. Only four cases had disease acquired during the previous two years.

In carrying out our toxicity studies, we were curtailed to a great extent by the fact that we were dealing with mentally ill patients who were incapable of giving the cooperation necessary to obtain accurate results in many of the known laboratory procedures. It was therefore decided that one reliable test for kidney function as well as one dependable method of checking liver function would be adequate to determine whether any damage to these organs was being incurred as the result of administration of this drug. Additional measures were tried but had to be abandoned because results were so variable and inconsistent that it was thought that they would confuse the issue rather than contribute information.

The results of these examinations made before and after 90 days of administration are as follows:

1) Bromsulphalein test for liver function: While seven patients in this group showed slightly abnormal dye retention prior to administration of the drug, only two of them had an increased impairment after 90 days of treatment. The others not only failed to show any increase in apparent liver damage, but the dye retention actually decreased to or

TABLE I: DISTRIBUTION OF CASES

Age Group	Number of Patients	Minimal	Mod. Adv.	Far. Adv.	Average Duration Years
21-30	3	0	2	1	2.6
31-40	11	1	4	6	4.5
41-50	12	1	1	10	7.0
51-60	8	0	6	2	9.0
Over 60	14	0	7	7	6.6
TOTAL	48	2	20	26	6.4

below the upper limits of normal. Two other patients showed slightly abnormal retention of dye after 90 days of treatment. In spite of this finding we were unable to demonstrate clinically any evidence of acute liver damage in these patients. Another had acute jaundice after 25 days of treatment, and because of this, medication was temporarily discontinued. After 10 days the jaundice subsided, administration was resumed and the patient was continued on for the remainder of the 90 days without a recurrence of jaundice. Liver function tests on this patient showed no evidence of damage after 90 days of treatment. Since there were similar cases of jaundice at the same time among other patients not under treatment with the drug, this was obviously an acute hepatitis in no way related to the medication which the patient was receiving.

2) The 24-hour urine concentration test after being evaluated showed no changes which we would interpret as representing evidence of renal damage. An impaired ability to concentrate was present in five cases before isonicotinic acid hydrazide administration. No increase in impairment could be shown after 90 days and no other evidence of further renal damage was noted.

3) An overall review of the blood study would indicate that hemopoiesis suffered no interference but rather that there was an apparent stimulation taking place while treatment was being carried out, as evidenced by increases in erythrocyte counts and hemoglobin values in 24 patients (50 per cent of cases). While six patients who demonstrated mild leukocytosis in the pretreatment examination showed reduction in white cells during treatment, the study of the leukocyte counts indicated that there was no frank tendency to leukopenia.

It is therefore our belief, as a result of these studies on liver function, kidney function and blood, that isonicotinic acid hydrazide administered in a daily dosage of 4 milligrams per kilo of body weight for 90 days does not produce toxic or degenerative effects upon those structures.

Concerning the effects noted with regard to changes in the x-ray film of the chest and the presence or absence of tubercle bacilli in gastric washings, we report the following:

1) Marked improvement was noted in one, moderate in three, slight in 14 patients and the remaining 30 showed no improvement or a definite progression of disease by x-ray evidence.

2) Reports on gastric lavages taken after 90 days of treatment show that 11 patients who had previously been consistently positive, had specimens from which acid fast bacilli were not recovered on culture.

Our results in this respect do not, therefore, parallel those of other investigators,[2,3] and we feel that this finding may in some way be related to the type of patients under consideration in this series.

Under the heading of side effects, we have included changes with reference to patient's weight, appetite, erythrocyte sedimentation rate values

and changes in body temperature elevation. The following changes were observed:

1) Some degree of appetite improvement was seen in more than two-thirds of the patients treated. Three showed marked, 20 had moderate increase, 11 slight improvement and in 14 there was no apparent change.

2) Twelve patients failed to gain but actually lost weight. Of the remaining patients eight gained more than 10 pounds, 11 showed weight increase ranging from five to 10 pounds and 17 had increases of five pounds or less.

3) Erythrocyte sedimentation rate decreased in 37 patients after 90 days of treatment but normal values were obtained in only eight cases which previously had abnormal rates.

4) Eleven patients still had slight to moderate afternoon temperature elevations after 90 days. Thirty-seven showed normal temperature curves.

One additional side effect relates to two diabetic patients who were included in the group: One of them, who consistently showed a 4-plus reaction for reducing substances in the urine has, while under treatment with the drug, repeatedly shown a decrease in the amount of reducing substances in his urine specimens. Many of the specimens tested showed a complete absence of reducing substances. This is of interest in view of the fact that during this period there was no increase or decrease in either the caloric intake or the amount of insulin used daily by the patient. A second diabetic patient showed a similar response and on one occasion during the course of the treatment, while on the same diet as previously given and with no increase in the amount of insulin administered, was seen in a state of insulin shock from which he made a rapid recovery following the administration of glucose. While we are ready to concede that the decreased glycosuria in these patients probably is on the basis of an elevated renal threshold for sugar, it is difficult to rationalize concerning the state of hyperinsulinism which was suffered by the second patient. It should be pointed out that fasting blood sugar determinations were taken on both of these patients at weekly intervals and failed to show any appreciable reduction in blood sugar values. It is therefore not our aim to make any evaluation of the effects of this drug on diabetics even in the face of these findings and even though one of the diabetic patients showed a most remarkable anti-tuberculous response to the drug as evidenced by the appearance of his chest x-ray film following 90 days of treatment.

Probably the most interesting side effect which we noted was the change in mental behavior in the group of psychotic patients under investigation. As was pointed out previously, these patients were chosen on the basis of their tuberculosis status and not on the basis of mental condition. Consequently, the group included a variety of mental diagnoses. Table II lists the patients with mental diagnosis and shows the degree of change in mental behavior which was noted during the course of drug administra-

tions. In arriving at the evaluation of the individual patient's mental condition, we accepted the diagnosis as made previously by the psychiatrist and as stated in the patient's record. We should like to stress the point that this was an unexpected and purely casual observation made during a study designed for an entirely different purpose. Therefore, the absence of controls is obvious, since we did not anticipate any such finding and to the best of our knowledge such changes have not been described previously. It might be well, however, to point out that all of those patients who showed any degree of improvement whatsoever, had previously received extensive medical treatment, including intramuscular streptomycin and oral para-aminosalicylic acid in courses ranging from 60 to 150 days. Under such treatment none had ever shown any visible change in mental behavior regardless of whether or not a change in general physical condition occurred. This fact, we believe, should serve to some extent as the equivalent of a control series and is also a strong argument against any claim which might be made to the effect that the changes noted here in mental behavior were purely on the basis of suggestion or increased attention received by the patient during the course of treatment. The changes which

TABLE II

MENTAL DIAGNOSIS	NUMBER OF PATIENTS M	F	Total	BEHAVIOR IMPROVEMENT Marked	Moderate	Slight	None
Dementia Praecox, Paranoid	8	7	15	1	5	2	7
Dementia Praecox, Catatonic	2	2	4	0	1	1	2
Dementia Praecox, Hebephrenic	4	3	7	2	1	0	4
Dementia Praecox, Simple	4	5	9	2	3	0	4
Paranoid Condition	1	0	1	0	0	0	1
Psychosis with Mental Deficiency	1	3	4	1	1	0	2
Psychosis with Paralysis Agitans	0	1	1	0	0	0	1
General Paresis	0	1	1	0	0	0	1
Psychosis with General Arteriosclerosis	1	0	1	0	1	0	0
Psychosis, Senile Paranoid	1	0	1	0	0	0	1
Mental Deficiency	0	1	1	0	0	0	1
Manic Depressive	1	0	1	0	0	0	1
Without Psychosis	2	0	2	0	0	0	2
TOTAL	25	23	48	6	12	3	27

we list as improvement in mental behavior could not in all cases be considered an improvement from the social standpoint, since we have included such changes as spontaneous activation in catatonics even though this might be of a belligerent nature. This latter change is, nevertheless, considered to be an improvement from the psychiatric point of view, and in most of the cases listed, the improvement was such as to be classified socially acceptable at least to some degree. The improvement is, in our opinion, more than a temporary feeling of euphoria or increased sense of well being. In some of our cases, it actually appears to represent a renewed contact with reality in patients who have been withdrawn and hallucinated for a prolonged period. Among the group of patients showing no change in mental behavior, many were only mildly psychotic and displayed no gross evidence of psychosis. We should like to call attention at this time to the fact that the greatest degree of improvement occurred, as a general rule, among patients with a diagnosis of schizophrenia, without any significant relation to the type. Since it is not our purpose here to assume the role of the psychiatrist but rather to point out that we have observed a change in mental behavior which we feel is directly related to the administration of isonicotinic acid hydrazide, individual case reports have not been included. We are simply reporting these changes in the hope that we may stimulate an interest in further research into this interesting phenomenon.

SUMMARY

Isonicotinic acid hydrazide was administered to a group of 51 mentally ill tuberculous patients in an effort to assist in determining whether toxic effects to the liver, kidney and blood forming organs would be encountered during the course of treatment. Two patients had to be discontinued because of the lack of cooperation and one with severe pulmonary and superimposed renal tuberculosis died after a short period of treatment. All treated had known active tuberculosis at the time administration of the drug was begun. The conclusions reached as a result of this study are as follows:

1) There was no demonstrable damage to the liver, kidney or blood forming organs after 90 days of treatment and it was not thought that those patients showing damage prior to treatment had any significant increase in impairment of function which could be related directly to the action of the drug.

2) Increase in appetite and weight and reduction in sedimentation rate were in keeping with findings as reported elsewhere but did not parallel in degree those published by other investigators. This probably is related in some way to the type of patient treated in this series.

3) Study of chest x-ray films and gastric washings after 90 days of treatment showed no consistent x-ray improvement but 22.9 per cent of cases treated showed change in sputum status.

4) An improvement in the mental behavior of psychotic patients under treatment with this drug was noted in a reasonably high percentage of cases.

RESUMEN

Se administro la hidracida del ácido isonicotínico a un grupo de 51 enfermos mentales tuberculosos con el fin de determinar si se encontraban efectos tóxicos sobre el hígado, el riñón y los órganos hematopoyéticos, durante el tratamiento. En dos enfermos hubo de interrumpirse el tratamiento por falta de cooperación de ellos y en el caso de otro enfermo había grave tuberculosis pulmonar con tuberculosis renal y murió a poco de empezado el tratamiento. Todos los casos tratados tenían tuberculosis averiguada antes de que se les proporcionara la droga. Las conclusiones a que se llegó después de este estudio son las que siguen:

1) No hubo daño demostrable en el hígado, riñónes u órganos hematopoyéticos, después de 90 días de tratamiento y no se cree que en aquellos que tenían daño previo al tratamiento, este haya causado aumento significante de ese daño o trastorno funcional en relación directa con la acción de la droga.

2) El aumento del apetito y del peso y la reducción de la sedimentación globular se asemejaron a los encontrados en otras partes pero no pueden parangonarse con los publicados por otros investigadores. Probablemente esto se debe en parte al tipo de enfermos tratados en este grupo.

3) El estudio de las películas de rayos X, de torax, y los lavados gástricos, después de 90 días de tratamiento no mostraron importante en los rayos X pero el 22.9 por ciento mostraron conversión de sus esputos.

4) Se notó una mejoría en la conducta mental de enfermos psicóticos en un porcentaje de casos razonable.

RESUME

L'hydrazide d'acide isonicotinique a été administré à un groupe de 51 malades mentaux atteints de tuberculose. Cet essai devait permettre de déterminer si l'effet toxique de ce produit allait atteindre le foie, les reins ou les organes hématopoiétiques au cours du traitement. Deux malades ne purent poursuivre le traitement parce qu'ils ne purent s'y soumettre, un autre, atteint d'une tuberculose pulmonaire et rénale grave mourut après un court essai thérapeutique. Tous les malades traités avaient une tuberculose évolutive connue lorsqu'on commençà l'administration du produit. Les conclusions qui résultent de cette étude sont les suivantes:

1) Il n'y a pas eu d'atteinte évidente du foie, des reins ou des organes hématopoiétiques après 90 jours de traitement. En outre, on n'a pas eu l'impression que les malades qui semblaient avoir des altérations antérieures au traitement montrèrent un accroissement de leurs troubles que l'on puisse rapporter directement à l'action de la drogue.

2) L'augmentation de l'appétit et du poids, la réduction de la vitesse de sédimentation furent constatées, en accord avec ce qui à été rapporté ailleurs, mais ne se montrèrent pas au degré que certains chercheurs ont publié. Il est probable que ces constations s'expliquent dans une certaine mesure par la catégorie particulière des malades qui ont été choisis pour être traités.

3) L'étude des clichés thoraciques, et des tubages gastriques après 90 jours de traitement ne montra pas d'amélioration radiologique, mais 22.9% des cas traités montrèrent des modifications des crachats.

4) En constata une amélioration de l'attitude psychique des malades mentaux traités avec ce produit, dans un pourcentage de cas nettement élevé.

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Double Aortic Arch Associated with Coarctation of the Aorta: Surgically Treated Patient

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Anomalies of the aortic arch system may assume many different anatomic patterns. Some are only of academic interest; others are of extreme clinical importance and may at times constitute an emergency requiring prompt surgical intervention to save life.

The anomalies of the aortic arch system which produce symptoms and which require surgical treatment are of three types. First, there are the "vascular rings," which are so disposed as to form a ring around or to press against the trachea, the esophagus or both; second, those anomalies which produce obstruction in one or another part of the aorta, namely coarctation; and third, persistent patent ductus arteriosus.

The surgical correction of coarctation of the aorta has become a standard procedure and is ideally performed on young adults; occasionally this anomaly produces cardiac symptoms in early life necessitating surgical treatment to avert progressive, at times rapidly progressive, heart failure.

The patient on whom data are reported here had the unusual combination of a vascular ring in the form of a double aortic arch with stenosis of the right (posterior) arch and coarctation of the left (anterior) arch.

Report of Case

A man, 25 years old, came to the Mayo Clinic in November 1951, for surgical treatment of coarctation of the aorta, a condition diagnosed elsewhere 10 years previously. Hypertension had first been discovered during the course of a routine examination in 1937 when he was 11 years old. He had enjoyed excellent health and even though he knew about the hypertension and its cause, he was active in sports which included four years of college football. The patient was unusually well developed, being 6 feet (about 183 cm.) in height and weighing 205 pounds (about 93 kg.). The blood pressure in the right arm was 204 mm. of mercury systolic and 100 diastolic, and in the left arm 210 systolic and 104 diastolic. No pulsations could be felt in the abdominal aorta or in the femoral arteries. There was a systolic murmur over the base of the heart without any appreciable increase in the size of the heart clinically. A routine roentgenogram of the thorax revealed questionable "notching" of ribs (Figure 1). Roentgenoscopic examination revealed some enlargement of the left ventricle. During this examination it was noted that the esophagus was displaced anteriorly, apparently by a retro-esophageal vessel. The electrocardiogram showed a rate of 72, sinus rhythm, notched QRS waves in lead III, notched P waves in lead II, diphasic P waves in lead III, inverted T waves

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in leads III and V-1, positive T waves in leads V-2, V-3 and V-4 and positive T waves and small Q waves in leads V-5 and V-6.

It was appreciated then that, while we were dealing with a coarctation of the aorta, there were present also other anatomic deviations from the normal, not usually seen in cases of coarctation of the aorta. Routine laboratory examinations contributed no additional significant information.

Although it was appreciated that this was not a perfectly typical instance of coarctation of the aorta we felt that exploration of the lesion with resection of the strictured segment of aorta and anastomosis, if feasible, should be carried out. Accordingly operation was performed on November 24, 1951, by one of us (Clagett). A long curved incision was made around the tip of the scapula and carried high enough posteriorly to permit resection of a long segment of the fifth rib and a short segment of the fourth rib. The patient was a large, remarkably well-developed athlete with powerful shoulder girdle muscles. As usual in cases of coarctation there was an extensive collateral circulation throughout the site of incision.

When the pleura was opened, the findings were typical for coarctation of the aorta, with the stricture of the aorta involving a left aortic arch and occurring about 2 cm. below the origin of the left subclavian artery and about 0.5 cm. below the ligamentum arteriosum. The internal mammary arteries and intercostal arteries were large and tortuous. On first inspection this was a perfectly typical coarctation of the aorta. We proceeded with dissection. The first three left intercostal arteries below the stricture were ligated and divided, and the ligamentum arteriosum was ligated and divided. As dissection was carried around behind the aorta it became apparent that there was a large vessel arising from the posterior wall of the aorta just below the site of coarctation. It was first assumed that this was a large right intercostal artery. Further dissection disclosed, however, that this vessel extended upward and posteriorly and that it was, in fact, the posterior or right arch of a double aortic arch (Figure 2). Occlusion of this vessel did not affect pulsation of the right radial artery. It was a large vessel, almost as large as the anterior aortic arch; however, it narrowed at its junction with the descending thoracic aorta. The presence of this vessel seriously complicated any attempt to resect the coarctation and perform an end-to-end anastomosis. At first we

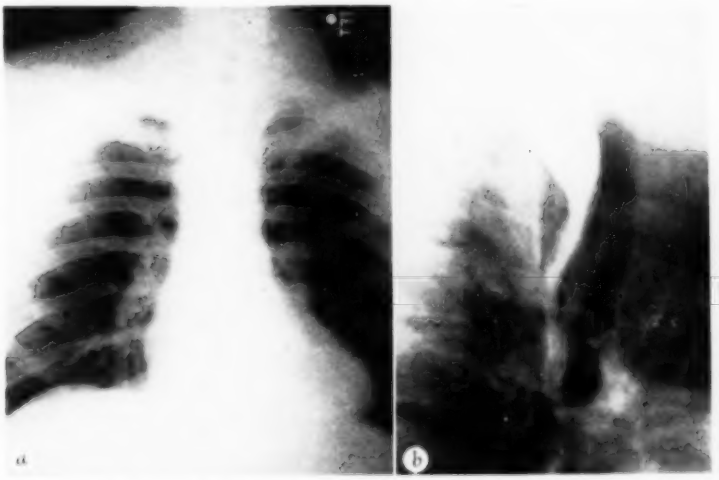

FIGURE 1a FIGURE 1b

Figure 1a: Roentgenogram of thorax.—*Figure 1b:* Esophagogram.

considered leaving this vessel undisturbed and proceeding with resection of the coarctation and anastomosis. However, in the course of dissection and mobilization the retro-esophageal vessel ruptured at its junction with the aorta. The proximal end was therefore ligated, and the aortic wall was repaired. The coarctation was then resected, and an end-to-end anastomosis of the aorta was performed.

The segment of aorta removed at operation had an appearance similar to that in the usual case of aortic coarctation in which resection is done for this disease.

FIGURE 2a: Operative area. L.A. = left aortic arch. R.A. = right aortic arch. D.A. = descending aorta. The first three left aortic intercostal arteries have been ligated and divided. The coarctation, involving the left arch, is partly hidden by the stump of the first aortic intercostal artery.

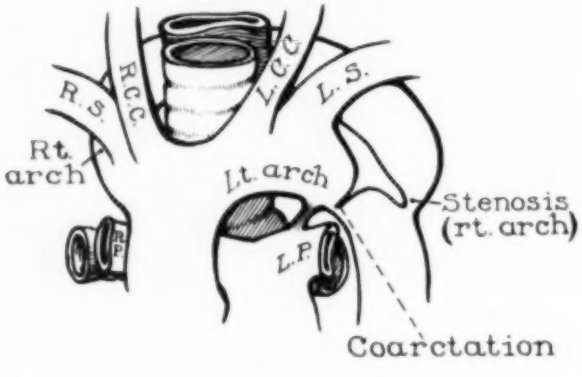

FIGURE 2b: Diagrammatic interpretation of findings at operation.

The specimen measured 1.2 cm. in length. Two millimeters distal to the aortic insertion of the ligamentum arteriosum there was a concavity involving the superior, anterior and posterior walls of the aorta. The wall into which the ligamentum inserted was not deformed. The external diameter of the aorta at the level of the deformity was 0.9 cm. Corresponding to this deformity seen externally was a diaphragm-like membrane across the aortic lumen. Grossly no lumen could be identified at this point.

Microscopic examination revealed the typical deformity of aortic coarctation (Figure 3). The media of the superior, anterior and posterior portions of the aortic wall protruded as a curtain into the lumen of the vessel and constituted part of the diaphragm observed grossly. The basic cause of the luminal narrowing was the deformity of the aortic media. Superimposed on this layer was laminated connective tissue containing elastic tissue. This tissue, which is considered to be acquired tissue, added in a minor degree to the narrowing of the lumen caused by the medial change. No lumen could be identified in serial sections of the specimen.

The patient's postoperative course was uneventful, and he was dismissed from the hospital on his twelfth postoperative day and from our care two days later. He was advised to restrict his physical activities for three months and permanently to avoid strenuous physical exertion. Whereas his brachial blood pressure had been recorded as more than 200 mm. of mercury systolic and more than 100 diastolic preoperatively, his postoperative pressures while in the hospital were recorded as 160 mm. of mercury systolic and 90 diastolic. His abdominal and femoral pulsations were readily felt postoperatively.

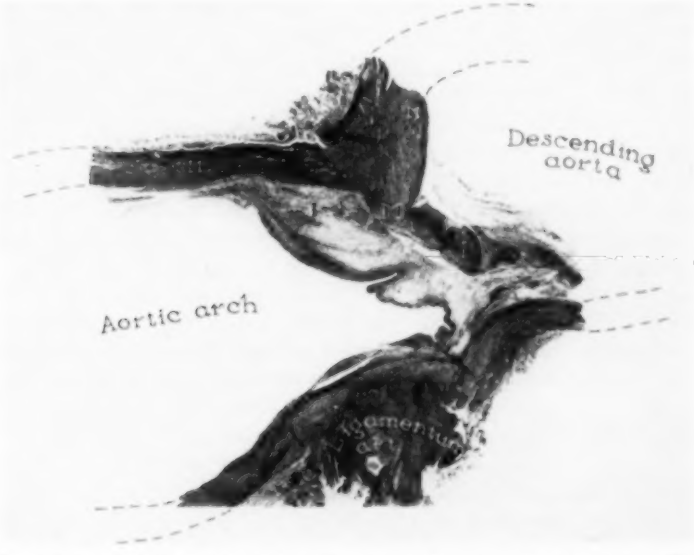

FIGURE 3: Longitudinal section of aortic segment removed during operation. Picture is characteristic of coarctation. The lower wall of the aorta, which receives the ligamentum arteriosum (ligamentum art.), is regular in contour. The superior wall shows characteristic infolding of the media (M), producing the basic narrowing of the lumen. Considerable superimposed intimal tissue (I) is proximal to the coarctation and at the coarctation. This tissue, which in part contains laminated layers of elastic tissue, narrows the lumen in excess of that caused by the medial deformity and obliterates the lumen (Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain, x 5½).

Comment

Persistent patency of the ductus arteriosus is not an uncommon companion of coarctation of the aorta, occurring in about 10 per cent of clinically recognized examples of coarctation. Other significant malformations of the great vessels in association with coarctation, of which the case herein reported is an example, are, however, rare.

This case of double aortic arch with coarctation of the left arch and stenosis of the right arch has some resemblance to two of the necropsied cases on which data have been analyzed by Arkin.[1] In each of these the roentgenologic evidence had suggested the presence of a double aortic arch, a condition verified by necropsy. In one of Arkin's cases the left arch had a short atretic segment beyond the left subclavian artery and proximal to the ligamentum arteriosum. The right arch was widely patent, not showing any point of stenosis like that exhibited in our case. The atretic segment of the left arch in Arkin's case may have represented coarctation; but, since no report of the microscopic appearance of this segment of the left arch was given, it is impossible to state that the atretic portion of the left arch had the same developmental significance as in our case. In our case the narrow segment of the left arch had the characteristic microscopic appearance of coarctation.[2]

In Arkin's other case in which necropsy was performed there was also a narrow segment involving the left arch in the same location as in his first case. Here the narrow segment was almost 1 cm. long, a fact which makes it unlikely that coarctation which would fulfill existing microscopic criteria existed here.

Regardless of the nature of the narrow segment involving the left component of a double aortic arch in each of the two of Arkin's cases mentioned, it is to be emphasized that the right arch was widely patent and therefore the clinical features of coarctation were not present in his cases.

It is pertinent to mention another, and yet rarer, malformation which may occur with coarctation of the aorta and yield signs of esophageal compression. This is the condition in which the right subclavian artery arises anomalously as the fourth branch of the aorta and below the coarctation. The artery then passes behind the esophagus to reach the right side of the body. A case of this type was represented in the review of Fawcett[3] (case 12), and a similar case of Stephens was mentioned by Gross.[4]

More recently, Sealy[5] described a similar case (case 1), the patient being a 19-year-old man, in which the anomalous right subclavian artery was demonstrated at operation. The coarctation of the aorta was proximal to the origin of the anomalous artery. The right subclavian artery was divided, and the segment of aorta containing the coarctation was resected followed by an end-to-end anastomosis of the aorta. It is of passing interest that as the right subclavian artery was clamped preparatory to division, and before the aortic coarctation was disturbed, the blood pressure in the right arm rose. As in the type of case herein reported there may be esophageal compression, but in the cases with the anomalous right subclavian

artery there are weak right radial pulses and low right systolic brachial blood pressures. In contrast, in our case with a double aortic arch the blood pressure and pulses in the two upper extremities were approximately equal.

Comment should be made about the absence of tracheal or esophageal symptoms in our patient with a vascular ring in the form of a double aortic arch. Many reports have emphasized the fact that this type of aortic deformity may give rise to alarming symptoms of respiratory obstruction in such cases and may cause death unless the ring is interrupted surgically.[6] At the same time there are reports of patients living a long and asymptomatic life with the same type of malformation.[7] Whether or not symptoms of tracheal or esophageal obstruction result from a vascular ring probably depends on the degree of compression of these two tubes by the vascular ring. As a rule, if symptoms occur, they appear in infancy or childhood. If no disturbances occur during this period, the vascular ring as such is usually of no concern to the patient. This was the case in the patient on whom data are presented. The reason for operation was evidence of intrinsic obstruction to the aortic channel rather than obstruction by the anomalous vessels to the structures they surrounded.

SUMMARY

The case of a 25-year-old man with double aortic arch, coarctation of the left arch and stenosis of the right arch is reported. The usual clinical signs of coarctation of the aorta were exhibited. A vascular malformation in association with the coarctation was suspected from the roentgenoscopic examination, which revealed esophageal compression in the upper part of the thorax. No symptoms of esophageal or tracheal dysfunction were present.

Treatment consisted in resection of the area of coarctation in the left arch with end-to-end anastomosis of this arch. The continuity of the right arch was interrupted. The postoperative course of the patient was good.

RESUMEN

Se refire un caso de un hombre de 25 años de edad con doble arco aórtico y estenosis del arcoderecho. Los signos habituales de la coartación de la aorta estaban presentes. Se sospechó una malformación vascular asociada a la coartación por el examen radiológico, que reveló compresión del esófago en la parte superior del tórax. No habia sintomas de transtorno funcional del esófago o de la tráquea.

El tratamiento consistió en resección del area de la coartación del arco izquierdo con anastomosis término-terminal de este arco. La continuidad del arco derecho fué interrumpida. La evolución postoperatoria del enfermo fué buena.

RESUME

Les auteurs rapportent l'observation d'un homme de 25 ans chez lequel existe un double arc aortique; il s'y asscie une coarctation de l'arc gauche et un rétrécissement de l'arc droit. On y constatait les signes cliniques

habituels de la coarctation aortique. L'examen radioscopique faisait envisager une malformation vasculaire associée à la coarctation. Il montrait en outre une compression oesophagienne dans la partie supérieure du thorax. Il n'y avait aucune manifestation clinique oesophagienne ou trachéale.

Le traitement consista en la résection de la zone de coarctation dans l'arc gauche, avec anastomose termino-terminale de cet arc. On supprima la continuité de l'arc droit. Les suites opératoires furent bonnes.

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The Use of 2-Ethylhexanol in Acute Pulmonary Edema

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The patient with acute pulmonary edema presents a picture of impending disaster. An agent with an effective antifoaming action might prove a valuable adjunct to accepted therapeutic measures. Survival during the initial critical period would be enhanced by permitting a more effective oxygen exchange in the alveolar tissues since a large amount of fluid in the respiratory passages can be tolerated as long as no foam is formed.[1]

Factors producing pulmonary edema include high blood pressure in capillaries of the pulmonary circulation, increased permeability of these vessels, decreased osmotic pressure, and neurogenic factors. Some drugs may be useful for one form of edema and may be contraindicated for another. For example, intravenous strophanthin may cause ectopic rhythms if given for this dire complication of coronary occlusion.[2] Venesection, spinal anesthesia,[3] merucrial diurectics,[4] and possibly morphine[5] may further reduce venous return and cardiac output during some shock states. Positive pressure oxygen is given during expiration and may be harmful in the presence of surgical shock or pulmonary emphysema.[6,7] Morphine, barbiturates and chloral are useful in cardiac patients but may exert a depressing action on the nerve centers when employed for edema owing to central nervous system injuries or inflammations. Hence, a therapeutic agent which could be employed in any case of acute pulmonary edema, regardless of the etiology, would be a useful adjunct. Recent experimental and clinical studies by Luisada have demonstrated that certain volatile substances decrease the foaming. He has employed ethyl alcohol in his work which has been substantiated by other investigators.[9]

An investigation of antifoaming agents employed in industry and in the laboratory suggested to one of us (N.E.R.) that 2-ethylhexanol had such possibilities for clinical use. The present study is concerned with the application of this substance by inhalation for the reduction of foaming in acute pulmonary edema.

Chemistry

According to Ross, 2-ethylhexanol is widely used as an antifoam agent in beet sugar production, paper manufacture, textile printing, glue spreading and elsewhere.[10] The substance is also known as octyl alcohol or octanol with the formula $C_4H_9CH(C_2H_5)CH_2OH$. It is a colorless liquid with a strong but not unpleasant odor. It is miscible with most organic

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solvents but practically insoluble in water. Also important is the fact that it is quite volatile, inexpensive and readily available.

Toxicity

Numerous studies have demonstrated that the substance is nontoxic. Although it is commonly used as an antifoaming agent in various industries, no poisonous effects on workers have been reported.[11] Nelson found that rats were unaffected after inhaling saturated vapors for a total of 150 hours.[12] Smith observed that the inhalation of saturated vapors for eight hours failed to kill guinea pigs. Two weeks later, autopsy revealed only slight congestion of the lungs and mild cloudy swelling of the kidneys in a few animals.[13] In another study, vapor exposure for an eight hour period caused no death among guinea pigs. Slight eye and nose irritation was observed in some of the animals.[14]

In our studies no harmful clinical effects were noted on 14 patients.[15] Since it has mild anesthetic properties, it is also beneficial in allaying apprehension. The substance has only one-sixth the toxic effect of ethyl alcohol when ingested.

Preliminary Studies

The antifoaming effect of 2-ethylhexanol was compared with that of 95 per cent and 50 per cent ethly alcohol. A soap suds medium was employed. Each substance was sprayed six times from an atomizer onto the surface of a measured soap suds solution (70 cc. water, 20 cc. liquid soap and 5 cc. green soap). A rapid foam fall occurred in the upper four-fifths, whereas a much slower fall was noted in the lower one-fifth in each instance. Similar studies were performed on the transudate from a patient ill with atrophic cirrhosis and ascites which was agitated to produce maximum foaming prior to testing. Control soap and transudate preparations remained almost completely foamy at the end of one hour. The results noted in Table I indicate that in *in vitro* studies, at least, 2-ethylhexanol exerts a more rapid effect than either 95 per cent or 50 per cent ethly alcohol when each is sprayed over foamed soap solution or transudate.

Method

In preliminary studies, manually operated nebulizers and atomizers were employed to deliver the mist or spray. There was a preference for

TABLE I: Relative Antifoaming Effects (Foam Fall) of 2-Ethylhexanol and Ethyl Alcohol (in Seconds)

ANTIFOAMER	SOAP SOL. 4/5 Fall	FOAM Complete Fall	TRANSUDATE FOAM Complete Fall
2-Ethylhexanol	15	40	4
95 per cent Ethyl Alcohol	45	170	38
50 per cent Ethyl Alcohol	180	incomplete at 6 minutes	incomplete at 2 minutes

the nebulizer because a finer particle was produced to better advantage. However, it was soon apparent that either method was inferior to a closed system. The mist or spray proved to be incompletely effective since the rapid respiratory rate made it impossible to expell manually the substance at the exact moment of each inspiration.

The closed system employed an ordinary BLB mask with the humidifier bottle half filled with non-miscible layers consisting of two parts water and one part 2-ethylhexanol. (Further studies are in progress utilizing full-strength 2-ethylhexanol which appears to be superior thus far). An oxygen tank with a rate of flow of nine litres per hour was used as the propellant. All other medication was withheld until the effects of this therapeutic measure were recorded (Figure 1).

Clinical improvement was judged from the following observations before and after inhalation. The presence of cough, cyanosis and apprehension was graded. The extent of pulmonary moisture was noted as well as the respiratory rate. The heart rate and rhythm and blood pressure was recorded. The time before appreciable clinical improvement was observed and personal comment by each observor was encouraged.

Selection of Cases

Any case of severe acute pulmonary edema, regardless of etiology, which came to the attention of the participating house staff at Kings County Hospital *before* other therapy was instituted was included in this study. There was a total of 14 unselected cases (13 males and one female). The

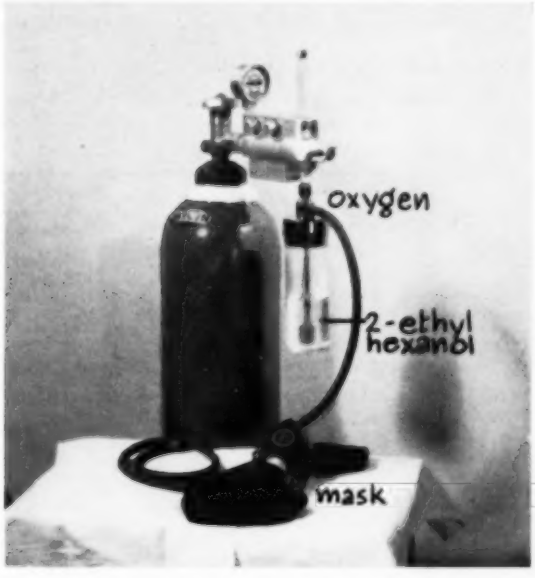

FIGURE 1

majority were past 60 years of age (Table II). This was the initial attack in half the patients (Table III).

Clinical Results

The duration of the attack prior to inhalation therapy is recorded in Table IV. It will be noted that the majority (9 cases) had pulmonary edema up to three hours before inhalation treatment was instituted.

The primary condition (Table V) was hypertensive cardiovascular disease in six, arteriosclerotic heart disease in four, combined hypertensive and arteriosclerotic heart disease in one, rheumatic heart disease in two, and meningitis in one. Diabetes mellitus was a concomittant factor in two patients.

The degree of clinical improvement noted for each disease process is listed in Table V. One patient with meningitis showed excellent clearing of pulmonary edema but expired suddenly after three hours from the primary disease despite intensive antibiotic therapy. A good therapeutic response was noted in 50 per cent of the patients. Of three who showed no improvement, one with rheumatic heart disease died before adequate inhalation therapy was instituted, and despite the fact that usual therapeutic measures (morphine, digitalis) were quickly added. The time interval before distinct improvement was noted is listed in Table VI. It will be noted that half had distinct relief within one-half hour while five appeared improved within 15 minutes.

TABLE II: Age Distribution

Years	Cases
30-39	2
40-49	0
50-59	1
60-69	7
70-79	2
80-89	2

TABLE III: Previous Attacks

	Cases
None	7
1	2
2	3
Not given	2

TABLE IV: Duration of Attack (Prior to Inhalation Therapy)

Hours	Cases
1-2	3
2-3	6
3-4	0
4-5	1
5-6	1
24	1
Over 24	1
Not given	1

Further studies are in progress employing 2-ethylhexanol in full strength and with oxygen under intermittent positive pressure. It is possible that beneficial effects may be expected in some cases of acute pulmonary edema due to choking gases, severe bronchial asthma, drowning, and other etiologic factors.

Illustrative Cases

Case 1: P.B., a 61 year old white male, had a long history of hypertensive cardiovascular disease with one previous attack of acute pulmonary edema. The present attack persisted for three hours, and was accompanied by cyanosis and apprehension. The respiratory rate was 36 per minute and bubbling rales extended to both apices. There was a sinus tachycardia with a rate of 140 per minute and the blood pressure was 220/106.

An excellent response was noted 15 minutes after 2-ethylhexanol inhalation was employed alone. The rales dropped to one-third their previous level. Cyanosis and apprehension disappeared. The pulse rate and respirations diminished to 120 and 26 per minute respectively. Blood pressure fell to 182/110. Digitalis and aminophyllin were then given with further improvement.

Case 2: J.C., a 67 year old white male, suffered from diabetes mellitus and arteriosclerotic heart disease for many years. He had had two strokes and was admitted in an unconscious state. There was no previous attack of acute pulmonary edema, and this one was present for five hours. Bubbling rales extended to both apices.

After three minutes of inhalation of 2-ethylhexanol, the pulmonary rales cleared to the extent that they were heard only at both bases. Conventional measures (morphine, digitalis and oxygen) were then applied with continued improvement.

Case 3: J.W., a 51 year old white male, with hypertensive cardiovascular disease suffered an attack of acute myocardial infarction. This was followed by the appearance of acute pulmonary edema which progressed to both apices within two

TABLE V: Diagnosis and Degree of Improvement

Etiology	Cases	None	Slight	Moderate	Marked
Hypertensive Cardiovascular Disease	6	1	2	2	1
Arteriosclerotic Heart Disease	4	1	1		2
Combined HCVD-As. HD	1				1
Rheumatic Heart Disease	2	1	1		
Meningitis	1				1
TOTALS	14	3	4	2	5

TABLE VI: Time of Relief

Minutes	Cases
1-15	5
16-30	2
31-60	0
Over 60	4
None	3

and a half hours. Cough, cyanosis and apprehension were present and the respiratory rate was 35 per minute. There was sinus tachycardia with a rate of 140 per minute and the blood pressure was 150/100.

Immediate relief was noted within several minutes following inhalation of 2-ethylhexanol and the rales cleared almost completely. The respiratory rate decreased to 30 per minute. The heart rate dropped to 100 per minute and the blood pressure fell slightly to 140/90. Subsequently, he was given oxygen under positive pressure, digitalis and aminophyllin. Unfortunately, he expired due to the severity of the myocardial infarction.

Addendum

Since this paper was submitted for publication, preliminary studies have been in progress employing nebulized 2-ethylhexanol in combination with oxygen administered from a positive pressure apparatus. Thus far, an effect superior to that obtained from the inhalation of 2-ethylhexanol vaporized in a humidifier bottle has been evident in 11 patients. The details of this investigation will be reported upon its completion.

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We are indebted to Dr. William Dock for valuable suggestions during the course of this study.

SUMMARY

1) *In vitro* studies indicate that 2-ethylhexanol has antifoaming properties superior to either 95 per cent or 50 per cent ethyl alcohol.

2) Fifty per cent of 14 unselected patients suffering from severe acute pulmonary edema due to various causes showed a good response to the inhalation of 2-ethylhexanol *before* routine measures were instituted. In some cases relief was dramatic.

3) There were no contraindications to its use and there were no toxic reactions.

4) The substance is volatile, readily available and easily applied.

5) Further studies are in progress with 2-ethylhexanol in full concentration and with oxygen under intermittent positive pressure with most encouraging results thus far.

RESUMEN

1) Los estudios in vitro indican que el 2-ethylhexanol tiene propiedades anti-espumigenas superiores al alcohol etílico ya sea al 95 por ciento o al 50 por ciento.

2) El cincuenta por ciento de 14 enfermos no escogidos, con severo edema pulmonar agudo debido a causas diversas mostraron una buena respuesta a la inhalación de 2-ethylhexanol, *antes* de que se emplearan las medidas habituales. En algunos casos el alivio fué dramático.

3) No hubo contraindicaciones para su uso y no hubo reacciones tóxicas.

4) La substancia es volatil, facil de obtener y facil de emplearse.

5) Estudios ulteriores estan indicados, incluyendo el uso del 2-ethylhexanol en concentración total y en mezclas con otros agentes antiespumígenos.

RESUME

Des études in vitro montrent que le 2-éthylhexanol a une action antisécrétante supérieure à l'alcool éthylique.

Chez 50% de 14 malades pris au hasard, atteints d'oedème aigu pulmonaire grave, d'origine variée, on a constaté une action favorable de l'inhalation du 2-éthylhexanol avant que fussent mises en train toutes les mesures thérapeutiques habituelles. Dans certains cas, l'amélioration fut spectaculaire. On ne signale ni contre-indication à son usage, ni réactions toxiques.

Il s'agit d'une substance volatile, rapidement efficace, et d'application facile.

Les auteurs font mention d'études ultérieures, et en particulier de l'usage du 2-éthylhexanol soit à l'état pur, soit associé à d'autres agents antisécrétants.

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The Duration of Carcinoma of the Lung*

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Considered a rare disease 30 years ago, carcinoma of the lung is today recognized as one of the common causes of death in individuals after the age of 40. It has been estimated that 10 per cent of all cancers occur in the tracheobronchial tree; by some authorities the respiratory tract is considered to be the third most common location for a fatal tumor.

Because of its protean nature cancer of the lung must be treated as an aggregate, rather than as an individual problem, if statistical validity is to be attained. In 1912, Adler[3] had an international collection of 374 known cases of carcinoma of the lung. Today series of thousands of cases are reportable and, in March of 1951, 624 lung cancers studied by the joint efforts of the Consultation Clinic of the Brompton and Royal Cancer Hospital in the five years from 1944 to 1948 were reported.[5] One year later, Ochsner, DeCamp, DeBakey and Ray[22] were able to report the details of 948 patients with bronchogenic carcinoma which they had personally observed. Today "cancer of the lung is the most frequent visceral cancer of the male patient," (Wynder and Graham, 1950[33]). Overholt predicts that present practicing physicians alone will contribute 3,500 lung cancers to this rapidly growing list.[23] A recent report from England and Wales shows that there were 15 times as many deaths reported from bronchogenic carcinoma in 1947 as in 1922.[5]

It is a natural reaction to question not only the reasons for this increase in international prominence but also its actual existence. Many authorities have suggested that the rising incidence was more apparent than real, or that it was a relative increase associated with the aging of our population. It is true that more people are reaching the visceral cancer age, but some other reason must be found to explain the elevation of lung cancer in men from eighth to first or second place.[13] It would be heretical to suggest that the master pathologists of the last century failed to recognize this tumor and it would be a derogation to suggest that our pathologists today recognize it only because of the notoriety brought to it by the radiologists and surgeons. The increase would seem to be real. The correlation of the increase in bronchogenic carcinoma with the increase in the use of tobacco as indicated by Wynder and Graham,[33] Ochsner, et al.[22] and others may or may not be valid but the increase in incidence is certainly true.

Bronchogenic carcinoma works stealthily for a portion of its life but

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once it announces its presence it proceeds with great rapidity toward the destruction of its host. That it works quietly is shown by the fact that 73 to 91 per cent "dig in" so firmly and extensively that they cannot be surgically attacked.[18,31] That it works efficiently is demonstrated by an average survival of the host given as 8.3 months in England,[5] and 2.4 to five months[1] in the United States. The brief time available for surgical rescue is emphasized by Overholt in his Monograph, "Cancer of the Lung,"[24] in which he shows how the sands of life run silently out of time's hourglass while the cancer becomes more and more firmly entrenched. Overholt and Schmidt[25] and subsequently Overholt[23] have emphasized the "silent phase" of bronchogenic carcinoma.

It is not surprising that the volume of writing about the pathology, histology, incidence, clinical findings and surgical treatment of carcinoma of the lung should be immense. It is a disease whose manifications are very wide. It touches upon the pathological physiology of the bronchi and lungs; it exhibits every variety of pulmonary pathology; it imitates and is imitated by practically all the abnormalities to which the lung is heir. It is surprising, however, that so little is known of the mode of onset, the development, the life history, what we please to call the biography of the disease. In the case of tumors it is usually impossible to determine the exact time of onset, when the abnormal cell appeared, when it began to multiply. It is important, however, to know how rapidly such lesions grow, how long after the onset will they cause the death of the host.

The answer to such a question cannot be obtained from the history given by the patient for the onset of symptoms is often a poor criterion of the onset of a disease. The surgical specimen is an end result, the autopsy findings are even more remote. If we were able to procure repeated biopsies through the bronchoscope or make numerous repeated examinations of the sputum for cancer cells, in apparently healthy individuals, we might get some answers as to the time of onset, but this is obviously impossible. Furthermore, in most cases, once the diagnosis becomes apparent, some form of therapy is instituted which interferes with the ordinary development of the disease. However, there are some cases in which an opportunity for study is afforded as a result of an error in the interpretation of the first roentgen examination, a failure to appreciate the importance of early symptoms, or the refusal of any therapy by the patient. As a result, repeated roentgen studies may be made over a period of time thus affording a visual demonstration of the course of the disease.

For many years we have been interested in the past history of patients with carcinoma of the lung with a view toward the elucidation of five important points:

1) What is the duration of the disease from its onset until surgical intervention or the death of the host?
2) What are the earliest manifestations of the tumor?
3) At what point in the history of the disease process is it possible to obtain roentgen evidences of abnormality?

4) What is the relationship between the onset of symptoms and the first appearance of positive roentgen findings?
5) What are the roentgen findings which characterize the early, pre-symptomatic stages of the disease?

In order to gain some insight into these questions, we have tried to obtain information as to the past roentgenologic history of patients with known carcinoma of the lung. For a number of years one of us has been tracing down and obtaining for comparison roentgenograms of the chest of such patients, made upon earlier occasions.[28,29] In most cases such roentgenograms have been made as a part of an industrial or public health survey of apparently healthy individuals, or as a part of the treatment of some other disease. With the widespread use of roentgen examination for the discovery of pulmonary tuberculosis and the frequent use of the roentgenogram whenever any type of pulmonary disease is suspected, it is not surprising that many patients should have had roentgen studies of the lungs on occasions prior to the onset of a presently existing illness. In some of these there were found clear-cut roentgen evidences of a disease process—later proved to be carcinoma—many months and, in some cases, many years prior to the onset of symptoms. After observing cases with positive roentgen findings seven and one-half, five, four and three years before the patient presented himself with the symptoms of the disease, we decided to investigate this biography more systematically. Accordingly, we set about to discover as many early roentgenograms of the chest as possible amongst a group of 264 proved cases of carcinoma of the lung.

Letters were written to patients, wives, relatives, family doctors, surgeons, hospitals and Public Health agencies begging for information. Of 142 such letters, 75 were answered, and of these 29 produced material of use or interest. Frustrating factors were many. Vagrancy made continued observation impossible in some cases. With the death of the patient the wife usually moved, often without leaving a forwarding address, and sometimes she kept moving, living first with one of her children, then another. Some of the wives had died, while others had difficulty with senescent memories. The family doctor often had no x-ray films or had sent them to a surgeon or a hospital. Surgeons and hospitals often returned their films and records to their point of origin so that some seemed forever in transit. Some large clinics destroyed their roentgenograms. Perhaps the greatest disappointment came from the Public Health and mobile chest survey organizations who sometimes destroyed, but more often lost the records, apparently through administrative difficulties.

At last from the 264 pulmonary cancer cases, we collected 50 histologically corroborated cases in which a roentgenogram accidentally antedated the advent of the identifying symptoms or signs. No other factor than this chance roentgen examination prior to the time the patient became ill was used in the selection of these cases. Amongst the 50, 34 are dead, three are still living but are dying of the disease, and 13 have been operated upon, thus interrupting the normal sequence of events. The first group

of 37 non-operated cases may be referred to hereafter as Group I. Group II refers to the series of cases that have had surgical intervention. All of these roentgenograms, viewed in retrospect, proved to have some evidence of the disease on or before the date on which the carcinoma could be clinically identified. In addition, we have some 15 other cases, collected at random, exhibiting similar findings.

A careful study of the history was undertaken to determine the date of the very earliest symptom. As can well be imagined, much difficulty was encountered here. For example, a great many of the patients had a so-called chronic cigarette cough for 10 to 20 years. The significance of this complaint must be minimized else it becomes impossible to point to any specific date as the beginning of the disease symptoms.

It should be noted that the interval of time from the beginning of symptoms, as dated by the patient, until death can be determined with fair accuracy, but this interval may frequently be greater than the actual duration of the symptoms due to cancer. Such exaggeration is due to the inability of the patient to distinguish between the co-incidental symptoms of other unrelated conditions and those symptoms associated with lung carcinoma.

The reverse is true of the roentgen signs. Mass survey and routine chest x-ray examinations do not always survey asymptomatic cases and in some of our patients, roentgenograms were not made before or even at the time of the initial symptoms or even at the onset of characteristic identifying symptoms. Symptoms can often be elicited post hoc, once a lung lesion is discovered. Even when the chest is examined at the opportune time for the discovery of asymptomatic carcinoma, the films may not be available for inspection. Despite these factors which tend to magnify the importance of symptoms and minimize the importance of roentgen signs, almost 75 per cent of a group, selected because x-ray examination had been made prior to any suspicion of the presence of carcinoma of the lung, were asymptomatic at the time the lesion was visible roentgenologically. The average interval between the registration of the first roentgen sign and the death of the patient must be much less than the true duration of the disease. Since three of the patients in Group I (non-operated) are still alive, the duration of the actual disease will be greater by an unpredictable amount than the average presented here.

Tumors subjected to radical surgery are collected in Group II since their course may be ended by the cure of the patient, or it may be prolonged by palliation of the patient, or a whole new set of abnormalities may be caused by the operation and speed the patient's demise. Therefore, in evaluation of evidence pointing to the length of tumor life, this group must be considered separately.

In Table I are exhibited the data on the 37 non-operated cases designated as Group I.

It should be noted that three patients give a "cold" as the first symptom. If this rather nondescript symptom were not considered, the average duration of symptoms would be appreciably shortened. It is also to be noted

TABLE I. GROUP I: MALIGNANT LUNG TUMORS FOLLOWED FROM INCEPTION

Case Number	Initial Symptom	Duration in Months	Roentgen Sign	Duration in Months	Cell Type	Duration of Cancer Dated Either From Earliest Symptoms or From Roentgen Signs in Months
1	Cough	23	Peripheral nodule	9	Squamous	23
2	Cough, dyspnea	24	Peripheral nodule	6	Oat cell	24
3	Weakness, cough	12	Hilum enlargement, emphysema	13	Oat cell	13
4	Cough	18	Hilum enlargement, emphysema	28	Squamous	28
5	Cough, anorexia	6	Emphysema	42	Oat cell	42
6	Chest pain, dyspnea	9	Nodule, left	9	Oat cell	9
7	Cough	7	Abscess	14	Squamous	14
8	Dyspnea, hemoptysis	14	Mass at base	22	Squamous	22
9	Cold	14	Peripheral nodule	11	Squamous	14
10	Dyspnea, weakness	7	Peripheral nodule	21	Small cell	21
11	Swelling side of neck	12	Hilum enlargement	9	Undiff. carcinoma, right	12
12	Cough	9	Peripheral nodule	35	Undiff. carcinoma	35
13	Cough, chest pain	12	Hilar mass, left	9	Squamous	12
14	Cough	19	Right hilum	20	Carcinoma	20
15	Hoarseness	5	Left hilum	8	Adenocarcinoma	8
16	Anorexia, weakness	8	Hilum enlargement	26	Adenocarcinoma	26
17	Cough	23	Peripheral nodule	29	Squamous	29
18	Cough	12	Mass, right lung	24	Undiff. carcinoma	24
19	Cough, dyspnea	26	Hilar mass, pleural effusion	29	Adenocarcinoma	29
20	Bloody cough	17	Left hilum	24	Squamous	24

TABLE I (Continued)

Case Number	Initial Symptom	Duration in Months	Roentgen Sign	Duration in Months	Cell Type	Duration of Cancer Dated Either From Earliest Symptoms or From Roentgen Signs in Months
21	Cough, hoarseness	7	Nodule, right lung	21	Adenocarcinoma	21
22	Cough, chest pain	12	Nodule, left	13	Squamous	13
23	Hemoptysis	12	Left hilum	14	Squamous	14
24	Chest pain	13	Nodule, left hilum	39	Adenocarcinoma	39
25	Chest pain, cough	18	Mass, left hilum	11	Adenocarcinoma	18
26	Pain left chest	11	Hilum enlargement	13	Squamous	13
27	Cough, chest tight	13	Peripheral nodule	12	Adenocarcinoma	13
28	Weakness, anorexia	9	Hilum enlargement	10	Squamous	10
29	Pain, dyspnea	4	Peripheral nodule	15	Carcinoma	15
30	Cough	12	Hilum, emphysema	31	Not listed	31
31	Cough	34	Cavity	34	Undiff. carcinoma	34*
32	Cold	18	Hilum enlargement	32	Squamous	32*
33	Cold	31	Hilum enlargement	22	Oat cell	31*
34	Cough	7	Peripheral nodule	14	Adenocarcinoma	14
35	None	0	Peripheral nodule	24	Squamous	24
36	Chest pain	8	Peripheral nodule	51	Squamous	51
37	None	0	Hilum enlargement	29	Squamous	29
	Average Symptom Duration	13.1	Average Roentgen Sign Duration	20.9	Average Cancer Duration	22.5

*Patient still living.

TABLE II, GROUP II: PULMONARY CANCER TREATED SURGICALLY

Case Number	Initial Symptom	Duration in Months	Roentgen Sign	Duration in Months	Cell Type	Duration of Cancer Dated Either From Earliest Symptoms or From Roentgen Signs in Months
1	Hemoptysis, Dyspnea	15	Peripheral nodule	15	Squamous	15
2	None	0	Peripheral nodule	29	Alveolar	29
3	"Pain", Cough	44	Peripheral nodule	45	Squamous	45
4	Cough	29	Peripheral nodule	35	Squamous	35
5	Pain	11	Enlarged hilum	13	Squamous	13
6	Discomfort	10	Peripheral nodule	53	Adenocarcinoma	53
7	Cough	108	Emphysema	109	Squamous	109
8	"Pain"	30	Enlarged hilum	31	Adenocarcinoma	31
9	None	0	Enlarged hilum	31	Squamous	31
10	None	0	Enlarged hilum	29	Squamous	29
11	Dyspnea	5	Peripheral nodule	7	Squamous	7
12	None	0	Enlarged hilum	29	Squamous	29
13	None	0	Enlarged hilum	12	Squamous	12
	Average Symptom Duration	19.4	Average Roentgen Sign Duration	36.4	Average Cancer Duration	36.4

that in this advanced, generally inoperable group there was only one case, discovered purely by roentgen examination, in which the patient had no symptoms whatever, even at the time the tumor was finally identified.

In Table II are exhibited the data on the 13 patients who were treated surgically.

As might be expected, the nature of the cases, which appeared to be operable, is markedly different. There are five cases in this group without any apparent symptom even at the time of surgical exploration. Despite this, the average duration is much longer both as to symptoms and roentgen signs. This finding suggests that the type of lung carcinoma which is susceptible to surgical treatment is likely to be a slow growing, relatively benign tumor.

Physical examination, the usual keystone of diagnosis, is of no value here, since tumors large enough to give physical signs are no longer in an early stage and are usually unresectable. Symptoms also are too little and too late. In many cases the first symptoms are those of distant metastases. The cigarette cough which plagues nearly all of these patients has already been discussed. It sometimes does happen that a second or third order bronchus is occluded, giving symptoms of dyspnea, often called "asthma." In these instances "trapped air" may be identified by percussion and auscultation, but the subsequent small patch of atelectasis usually eludes the best of clinicians.

It is worth noting that if we eliminate the symptom "a cold" as being significant, 20 per cent of our cases, including both groups, were discovered to have serious disease by reason of a routine roentgen examination. This represents a significant difference between our series and others previously reported. The Brompton Hospital of London Series,[5] for example, contained only 0.6 per cent of cases discovered by routine roentgen examination. In the series of 948 cases reported by Ochsner, et al.,[22] there were 332 cases in which resection was possible and only three of these were asymptomatic—less than 1 per cent.

The eliciting of symptoms is often difficult. But once the patient learns that he has a serious disease it is often possible to obtain a history of symptoms not previously given. Thus, nine patients who had no complaints at the time of the roentgen examination were found, in retrospect, to have had significant symptoms prior to the x-ray study. Of the 39 patients who were asymptomatic at the time of the first roentgen examination, 31 developed symptoms before the diagnosis was made or during hospitalization, while seven remained asymptomatic throughout the course to this date. In one instance, symptoms appeared coincidentally with the appearance of roentgen signs.

In reviewing the data it is observed that the longest duration of symptoms in Group I was 34 months. The longest duration of roentgen signs was 51 months. In Group II, the longest duration of symptoms occurred in a case with cough for 108 months. The significance of this might well be doubted except for the fact that there were roentgen evidences of localized emphysema, in the segment of lung later proved to be tumorous, present for an

even longer period. It is notable that in one case a peripheral nodule, easily observed, had been present for at least 53 months before the final diagnosis was established. Of the whole series, 12.6 per cent (including "a cold" as a significant symptom) were symptomless throughout the course of the disease until it was identified.

The average total duration of symptoms in the group of cases which were not interfered with surgically was 12.7 months. This corresponds closely with some reported series where comparable studies were made. Lindskog's[18] patients, on the average, had symptoms for 6.7 months before diagnosis and lived five months longer, if untreated, a total of 11.7 months. Churchill[6] gives one year as the duration of life from the discovery of the disease. Other data previously collected, as mentioned above, suggest that the duration of life after the inception of carcinoma of the lung is relatively short.

Roentgen signs of disease preceded the first symptoms by 7.8 months (average) in the patients in Group I. It is true that these signs were usually discovered in retrospect, but there can be no doubt about their presence. In Group II this discrepancy lengthened to 17.0 months between the average first detectable x-ray evidence of tumor and its clinical manifestations. Thus, in those patients selected for surgery the disease was either silent longer, or was more favorable to early x-ray detection, or both, by an interval of 9.2 months. It should be reemphasized here that the roentgen signs might well have been present for a much longer period of time since the first films were made fortuitously.

The duration of x-ray signs in the first group average 20.9 months. This is a longer cancer life than has ever been previously estimated. But all previous estimates were based upon the date of onset of the initial symptoms as the criterion for the presence of the tumor; the roentgen method has not been used previously in this manner. In the second group, the average duration of the disease as measured by roentgen signs was 36.4 months.

If one tries to estimate the duration of the disease using both symptoms and signs, and choosing the earliest evidences to appear, Group I average tumor life is stretched to 22.5 months. Save for isolated cases these are the longest average lung tumor life durations recorded.

Admitting the premise that carcinoma of the lung may be present without symptoms, and we can cite many advanced cases to prove it, it is evident that some new information about the life of this tumor has been found. In our two groups we have 39 patients who were asymptomatic at the time of the first roentgen evidence of the tumor. Traditionally, and in medical literature, the duration of the disease has been described as averaging between five and 11 months. But we find on the basis of our Group I cases a life history of 22.5 months. A new 10 months of life is offered, not to the patient, but to the radiologists, surgeons, and possibly the roentgen therapists in which to recognize and treat this lesion. It is entirely possible that the earlier treatment thus made available may preclude many of the metastases and much of the cachexia, may prolong

life, and decrease the morbidity from pulmonary carcinoma. But this cannot be achieved without more labor. Recognition and treatment of the disease in those 10 early months will require an increased alertness, suspicion, boldness and skill in order to see the tiny lesion, suspect its nature, remove it, and still not jeopardize the procedure. Over-diagnosis and over-treatment can bring even a sound approach into disrepute.

A consideration of the earliest roentgen signs and the changes observed in serial roentgenograms of the chest made on patients with carcinoma of the lung gives some information as to the earliest manifestations of the tumor, the possibilities of roentgen detection at an early stage, and the significance of certain changes in the roentgenogram. The earliest changes observed in the group of patients discussed above are as follows:

1) A nodular density in the lung periphery.
2) A solitary cavity or abscess in the lung parenchyma.
3) An area of infiltration along the vascular trunks.
4) Unilateral enlargement of the hilum shadow.
5) Segmental or lobar or even unilateral whole lung emphysema.
6) Minimal areas of atelectasis, usually linear in type.

From observation of serial roentgenograms made at semi-annual intervals of patients with non-pulmonary primary malignant tumors we have found that metastatic nodular lesions in the periphery of the lung are usually detectable when three millimeters in diameter, rarely so when only two millimeters in size. Similarly, the peripheral nodular lesion of primary carcinoma can be detected at an early stage. We have observed one case of squamous cell carcinoma in which a lesion three millimeters in diameter was visible. There were no symptoms. The lesion was overlooked but three and one-half years later another routine examination of the chest was made while the patient was still free of any symptoms. At this time the lesion was two centimeters in diameter and perfectly obvious. In another case, a lesion one centimeter in diameter was observed but thought to be a tuberculoma. Seven and one-half years later the patient first developed symptoms suggestive of the disease. At this time the lesion was large and typical of carcinoma. Obviously, there are occasional tumors, particularly those which prove to be of the undifferentiated variety, in which the growth is very rapid. An example of this type occurred in a patient admitted because of prostatic enlargement. There were no pulmonary symptoms but the routine film made on admission revealed a nodule 1.5 centimeters in diameter. Because of an error nothing was done about this and the patient was discharged after his prostatectomy. Nine months later he developed cough and hemoptysis which resulted in another roentgenogram of the chest. At this time the lesion already had filled most of the right upper lobe. As might be expected this tumor proved, on microscopic examination, to be a highly undifferentiated carcinoma.

From the cases observed we have found that the lesions which arise in the periphery of the lung gradually enlarge in concentric fashion (Figure 1) tend to extend toward the root of the lung (Figure 2), and finally produce lymph node enlargement. While the detection of such tumors is relatively

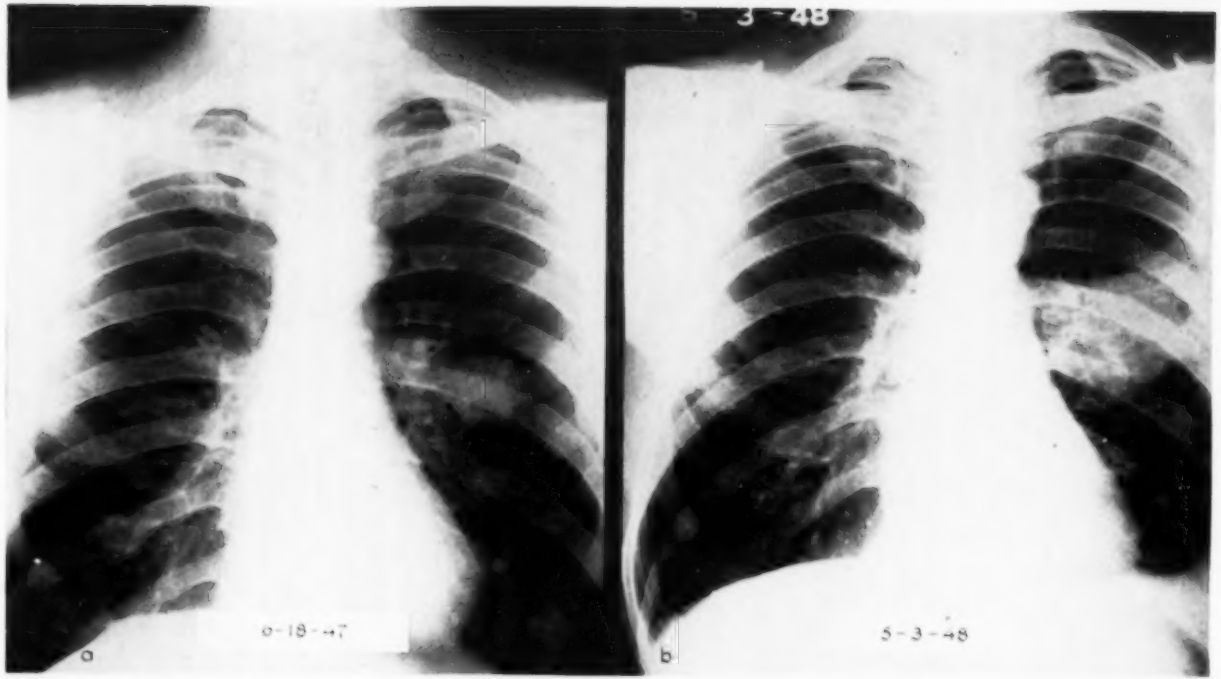

FIGURE 1 (Case 1): Carcinoma lung arising as peripheral nodule.—(**A**) Nodule in left lung, poorly defined, peripheral position, found six months earlier during chest survey.—(**B**) Extension of mass peripherally and centrally. Symptoms now present, 15 months after original x-ray finding. Pneumonectomy shows squamous cell carcinoma lingular segment left upper lobe.

easy their identification is particularly difficult. They are not likely to shed cells which can be detected by microscopic examination of the sputum. They cannot be reached by the bronchoscope. Body section roentgenography is helpful since it may permit the determination of the presence or absence of calcium within the lesion. If calcium is found it strongly suggests either hamartoma or tuberculoma. Every peripheral nodular density which does not contain calcium, especially if found in an individual over 50 years of age, should be considered a primary carcinoma until proved otherwise. Frequently local biopsy through the medium of a segmental resection of the lung or exploratory thoracotomy must be undertaken. Such lesions are readily detected by roentgen examination in their earliest stages. Many are now being found as a result of the routine examination of the chest of symptomless individuals. In the series here reported, 38 per cent were peripheral nodules.

The following two cases are presented as illustrations of the duration and progress of a nodular lesion.

CASE 1: A 50-year old male had an x-ray examination during a chest survey in January 1947. A "spot" on the left lung was found. He was symptomless at that time. The "spot" was considered of no significance by his physician; reexamination on June 18, 1947 (Figure 1A), revealed a nodule of fair size in the periphery of the left lung which was not sharply demarcated. Such a shadow in a 50-year old male is certainly an indication for exploratory thoracotomy but nothing was done. About a month later, some seven months after the nodule was first observed in the roentgenogram, he began to lose some weight. There were no other symptoms. In April 1948, 15 months after the original examination, cough, hemoptysis and chest pain first appeared. He came in for treatment one month later and a roentgenogram made on May 3, 1948 (Figure 1B), shows the nodule to have enlarged markedly in a concentric fashion, both peripherally and centrally. Pneumonectomy done at that time revealed a squamous cell carcinoma of the lingula of the left upper lobe. Patient is still alive and well.

Discussion: Such nodules as indicated above should never be ignored, but the fact that it could remain in the lung for a period of over 16 months before any procedure was undertaken and that the development of real pulmonary symptoms occurred 15 months after the first roentgen signs indicates the long duration of some lung tumors. At the time of surgery it appeared to be a thoroughly operable lesion and the fact that the patient is still alive four years thereafter indicates the relatively favorable character of the lesion despite the length of time during which we know it was present in the lung.

CASE 2: A 72-year old male was first found to have a "spot" in the right lung on a chest survey on July 22, 1949 (Figure 2A). It was apparently not considered of serious moment by his physician although the lesion was large and poorly defined. It was clearly a peripheral lesion and at the time when the first examination was made there were no symptoms and no evidences in the roentgenogram of obstruction of a major bronchus. The first symptom of weight loss appeared in March 1951, 20 months after the first roentgen finding (which was then already far advanced). The first roentgenogram when the patient appeared for definitive treatment was made April 16, 1951 (Figure 2B), and shows the characteristic atelectasis, retraction, and increased density of the right upper lobe which are so

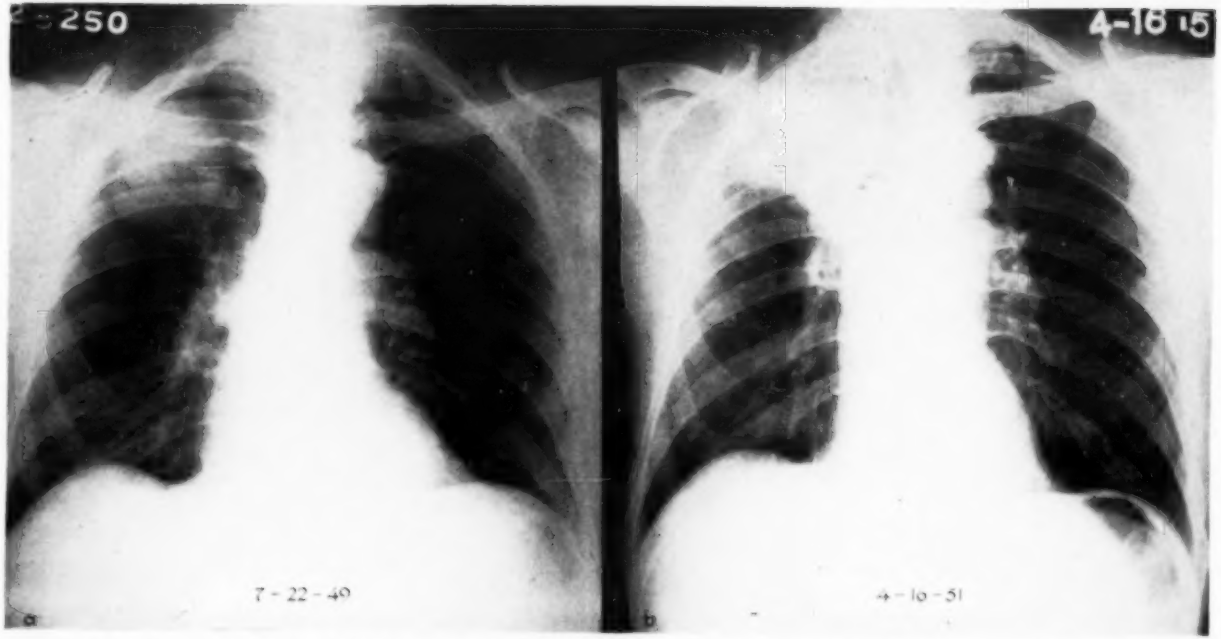

FIGURE 2 (Case 2): Carcinoma lung arising peripherally and extending into major bronchus. — (A) Mass in right upper lobe with poorly defined borders, peripheral origin, found during chest survey, no symptoms. — (B) Atelectasis right upper lobe from obstruction of bronchus. Symptoms began only one month before, 20 months after the first x-ray finding. The appearance here is characteristic of tumors arising in a major bronchus, yet the earlier film (A) indicates a peripheral origin.

common with obstructive bronchogenic carcinoma. Despite the minimal pulmonary symptoms, the patient already had metastases and operation was not done. He died June 4, 1951, and at autopsy an adenocarcinoma obstructing the right upper lobe bronchus was found. There were many metastases in various portions of the body.

Discussion: Such a case demonstrates clearly that a tumor arising in the periphery may extend centrally so that by the time of the autopsy it gives the impression of a tumor which arose primarily in the right upper lobe bronchus. This false impression of the origin of bronchogenic tumors has no doubt occurred many times because the only evidence available was that in the terminal stages of the tumor; it seems probable that many apparently peripheral lesions grow centrally and eventually produce obstruction, as was the case here. It is notable that the relatively minor symptoms did not appear until 20 months after the first lesion was seen in the roentgenogram.

A second finding, a rounded area of lesser density in the lung surrounded by a dense, ring-like shadow represents the necrotic abscess of a tumor. In contrast to the abscesses which appear in the atelectatic lung which results from bronchial obstruction, the cavity which results directly from tumor necrosis and ulceration usually stands alone, surrounded by normal lung. In its early stages the peripheral zone of density may be fairly thin but frequently at one point in this ring there will be found a small nodule or thickening producing an eccentric appearance. This is the most important identifying clue. Nevertheless any lung abscess in an individual of the cancer age, especially if there is no other good explanation for its presence, should be considered carcinomatous until proved otherwise. Fortunately these lesions commonly shed cells and the identification of the tumor may be made by means of microscopic examination of the sputum. As the lesion progresses many changes take place. The outer wall becomes thicker, more irregularities of nodular character can be seen along it, and dense masses appear within the gas-filled cavity itself. Such lesions are not observed for the long periods of time cited above since they are more malignant, spread more rapidly, and the diagnosis is more readily established so that some treatment is applied. Six per cent of the group showed an abscess as the first roentgen sign.

A third type of manifestation consists of an accentuation of the vascular trunks to such a degree as to suggest an interstitial infiltration. The appearance closely simulates fibroid tuberculosis but is more regular in its appearance. Patchy areas of a minimal degree of density appear. In addition, a few, small, nodular densities can be made out along the course of these apparently thickened vessel markings. While suggestive of an abnormal process, such changes are difficult to identify. As time goes on, the area of infiltration becomes large enough to present an appearance of consolidation; i.e., a more diffuse, homogeneous density appears. The lesions tend to radiate toward the hilum and the latter may enlarge at an early stage. Such tumors are usually thought to be inflammatory processes, in

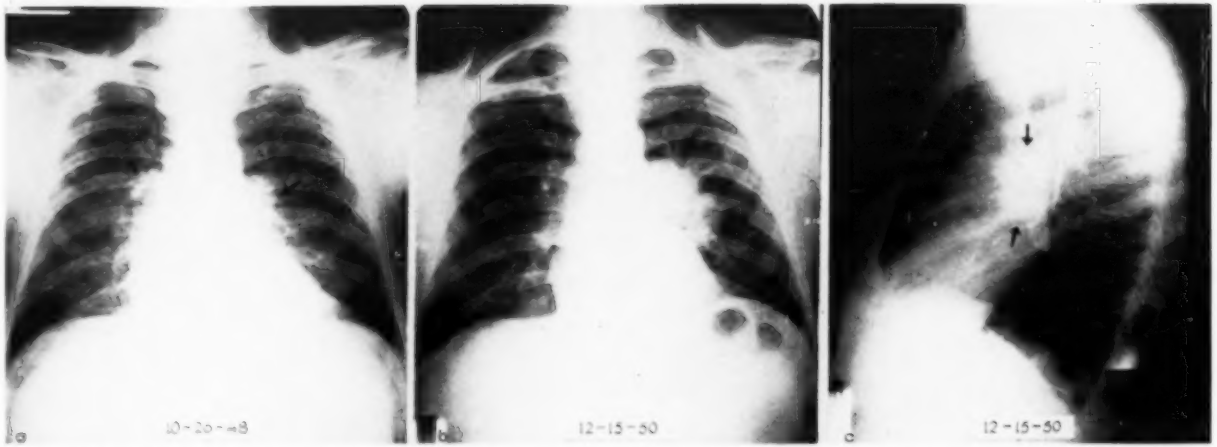

FIGURE 3 (Case 3): Carcinoma of lung producing enlargement of hilum shadow.—(**A**) First examination for cardiac symptoms. Note minor but definite enlargement left hilum (arrow). No pulmonary symptoms. — (**B**) Roentgenogram three months after onset of symptoms. Marked lobulated enlargement of hilum (arrows). Note sharp increase in size. (**C**) Lateral view demonstrates central position of shadow (arrows) indicating mass is in or around hilum.

their early stages, but the diagnosis of carcinoma should always be considered. The beginning enlargement of the root of the lung should identify their true nature. Only a very small number of such cases were found in our series.

Most important of all the roentgen signs found in this early stage of development is an enlargement of the hilum shadow of one lung (Figures 3 and 4). Forty-eight per cent of the cases were in this category. Furthermore, it is the most commonly overlooked sign. The shadow results from the extension of a tumor of a large bronchus into the peribronchial tissues or to the involvement of peribronchial lymph nodes. Nevertheless it may be a very early sign. An irregular enlargement of the hilum, particularly if it exhibits radiating linear areas of density around it, is extremely significant. Unfortunately there are marked variations in the normal hilum shadows. Furthermore, many non-tumorous lung lesions produce changes in the hilum. When the hilum appears abnormal, lateral, oblique and planigraphic examinations are very helpful. In this group particularly, comparison of films made at intervals, if they are available, is very helpful (Figure 3). Such tumors are commonly accompanied by evidences of bronchial obstruction but not necessarily so in their earliest stages. In any case, films should be made in both phases of respiration in order to accentuate any signs of bronchial obstruction which may be present. As time goes on the evidences of obstructive emphysema, followed by atelectasis, and then by the late inflammatory processes, which commonly result from bronchial obstruction, will be observed. In this group, as well, we have seen patients with clear roentgen evidences of the tumor as long as three years before symptoms appeared. In many cases, not until atelectasis supervened did the patient complain. Without doubt the unilateral enlargement of the root of the lung is the most important, the most frequent, and the most commonly overlooked early roentgen sign of pulmonary carcinoma.

Bronchial obstruction may be an early sign of tumors of the bronchus. Westermark reports that 96 per cent of 100 cases of proved carcinoma of the bronchus showed obstruction of some degree. Our experience does not bear out so high a figure but certainly bronchial occlusion is common and frequently is the very first evidence of the presence of a tumor. This is particularly true of the group of cases which show enlargement of the root shadow, in addition, but the evidences of obstruction may be present alone.

Occlusion of the bronchus from a tumor may result in a number of findings similar to those occurring with foreign bodies. Obstructive emphysema may be an early sign, as previously reported,[28] and was present in approximately six per cent of this small series (Figure 4A). It may be segmental, lobar, or may involve the entire lung. While often visible in ordinary postero-anterior roentgenograms made during inspiration it is best demonstrated in the expiratory phase, in some cases, only in films made during expiration.

The transition from emphysema to atelectasis (Figure 4) may be extremely rapid. We have been able to observe this in several cases in which

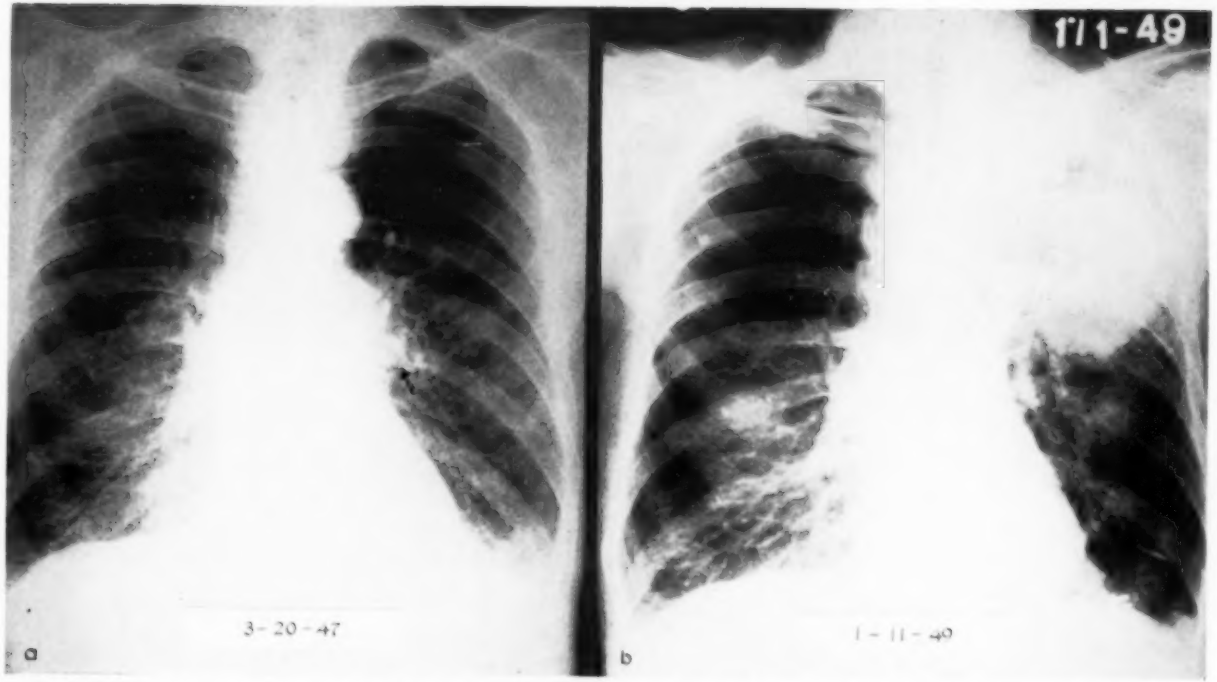

FIGURE 4 (Case 4): Carcinoma of lung manifested by enlarged hilum and segmental emphysema. — (A) Roentgenogram made because of chronic cough. Evidences of chronic bronchitis in both lower lobes. Minor but definite enlargement of the left hilum (arrows). There is also a marked emphysema in a segment of the left upper lobe.—(B) Reexamination 22 months later shows mass in left upper lobe, abscess cavity and further enlargement of the left hilum. Symptoms had been present for nine months prior to this time.

the diagnosis was not clearly determined and the patient was watched for a period of time. In one case about four months intervened from the first observation of emphysema until a complete atelectasis supervened in the same lobe. It is impossible, of course, to determine how long this period will last since cases are rarely recognized without some procedure being undertaken which prevents the development of the atelectasis.

Atelectasis is usually a late sign of bronchogenic carcinoma but in occasional cases occurs in a pre-symptomatic stage. Usually it is segmental and may be observed as a band-like or linear area of density in the roentgenogram. In studying such cases over a period of time, the contraction of a segment from a band-like or triangular shadow to a linear one is observed. As time goes on the tumor mass is seen and still later the usual lobar or unilateral density or a more extensive atelectasis.

The following two cases are reported to indicate the importance of minor degrees of enlargement of the hilum shadow and of the presence of emphysema as an early sign of carcinomatous obstruction of the bronchus.

CASE 3: A 65-year old, obese male, was first seen on October 21, 1948, with symptoms and signs of coronary disease. There were no definite pulmonary symptoms other than dyspnea and no physical signs in the lungs. A roentgenogram (Figure 3A) showed an enlarged heart. The left hilum was also enlarged but this was overlooked. In June 1949, an ulcerative lesion on the lower lip was biopsied and proved to be a squamous cell carcinoma. This was irradiated and later a neck dissection was done, two positive nodes being found. Reexamination of the chest was made on March 14, 1950, and showed further enlargement of the left hilum shadow. Again it was overlooked.

In October 1950, 24 months after the first x-ray evidences of an enlarged hilum, the first pulmonary symptoms, that is, a persistent "cold," cough, some sputum production and occasional hemoptysis, appeared. There was also some weight loss. The next roentgen examination was made on December 15, 1950 (Figure 3B), showing a massive enlargement of the left hilum. The enlargement had been very rapid in the past nine months. In the lateral view (Figure 3C) the shadow is seen to be actually in the hilum and not superimposed upon it from a lesion in the lung itself. Bronchography two weeks later showed a complete obstruction of characteristic type in the left upper lobe bronchus although on bronchoscopy the tumor could not be seen. The aspirated sputum was negative for tumor cells.

Pneumonectomy revealed a large squamous cell carcinoma of the left upper lobe bronchus, microscopically characteristic of a primary bronchogenic tumor. There were large lymph nodes in the hilum and invasion of the contiguous lung. The patient expired two days post-operative from coronary thrombosis.

Discussion: The progressive enlargement of one hilum shadow from a tumor is well illustrated here. Furthermore, the symptoms did not appear until several years after the first finding was observed. The course of events here was interrupted by surgery so that the period of 27 months is the minimum between the first x-ray evidences and the time of the fatal outcome of the lesion. It is notable that evidences of bronchial obstruction are not clearly apparent in the roentgenogram, even though by means of bronchography a fairly complete obstruction appears to be present. This is a common finding.

CASE 4: A 52-year old male was first seen on March 20, 1947, because of a cough of many years standing. The roentgenogram at this time (Figure 4A) revealed a distinct obstructive emphysema of the left upper lobe and a minor degree of en-

largement of the left hilum. There were also evidences of chronic bronchitis involving both lower lobes. For this reason the left upper lobe findings of emphysema were ignored and the enlargement of the hilum was thought to be of inflammatory nature. Six months later dyspnea began. Fourteen months after the first x-ray evidences, hemoptysis, cough and weight loss were first noted. Reexamination was made on July 3, 1948, and a marked density was noted in the region of the left upper lobe where emphysema had previously been present. The hilum shadow had increased somewhat in size. The density was thought to be due to pneumonia and nothing further was done. The thought that this was due to pneumonia was borne out by the fact that a month later the shadow in the left upper lobe seemed to decrease in size. This is a common error and is due to the fact that as the atelectasis increases, the compensatory emphysema of the other lobe increases as well so the shadow seems to diminish in size, for a time.

He was first admitted for treatment on November 30, 1948, complaining essentially of repeated attacks of influenza and pneumonia. At this time there was a large mass in the left upper lobe. A final film was made on January 11, 1949 (Figure 4B). This shows the extensive density involving the left upper lobe with a cavity within it. This no doubt represents both atelectasis and a very large lung abscess. The hilum shadow is covered to such a degree that it is difficult to observe its enlargement, but even so it appears to be distinctly larger than on the previous examination. The sputum showed characteristic cancer cells. He was considered inoperable and died on May 26, 1949, 26 months after the first evidences of the lesions observable in the roentgenogram.

Discussion: The changeover from emphysema to atelectasis is observed here and the final development of abscess formation in the atelectatic lung is also apparent. The first clue to this process was in the enlarged hilum and the emphysema accompanying it. In cases of this type in which there has been a chronic bronchitis with other changes in the lungs, the diagnosis becomes particularly difficult. Yet any enlargement of the hilum, especially if accompanied by evidences of obstructive emphysema or obstructive atelectasis, should be investigated to the fullest extent possible to exclude a carcinoma.

Obviously there are many other roentgen signs of carcinoma of the lung. We have discussed here only those found either in the pre-symptomatic stage of the disease or in roentgenograms taken a long time before the diagnosis became apparent.

It is evident from our experience that the routine or survey x-ray examination is the best and, in fact, the only applicable method for the early detection of pulmonary tumors. Roentgen evidence usually antedates symptoms, and in such cases periodic or routine chest films may exhibit lesions over two millimeters in diameter. The appearance of the lesion on the roentgenogram does not bring automatic recognition. It must be interpreted as an abnormal shadow, and someone must prod the asymptomatic patient into submitting to further, more definitive measures.

The human difficulties in interpretation of the roentgenogram can be decreased when control films of an earlier date are available for comparison of questionable shadows. Early tumors about the hilum are particularly hard to separate from normal root-shadow structures (Figures 3A and 4A). A firm knowledge of hilar anatomy and its normal variations becomes essential. This can be attained by planigraphy of the normal hilum, and

by examining plain roentgenograms in retrospect after large tumors have become evident. It is possible that mensuration of the hila with comparison will be helpful in establishing whether or not enlargement is present.[30] An appreciation of the urgency of the situation is more difficult to acquire. This factor must be more widespread before the cancer death rate can be expected to be reduced. That lesions were frequently overlooked is demonstrated by the fact that among the cases listed, 23 small hilar tumors went undetected until a later examination or the beginning of identifying symptoms. Three peripheral nodules were overlooked and four were misinterpreted as tuberculomas or chronic pneumonia. Localized emphysema was also overlooked. Small abscesses were likewise missed if medial in position, or misinterpreted if peripheral.

Silent carcinomas may be diagnosed by their appearance on the roentgenogram alone but frequently symptoms which seemed atypical or minimal are given greater significance when roentgen evidences become apparent. More advanced lesions may have their resectability as well as their identity betrayed by a chest film, but in the ordinary course of events this requires fluoroscopy to demonstrate functional changes, planigraphy to delineate the gross appearance and extent of the lesion, and bronchography to map its environs. Then, if histological confirmation is otherwise unavailable, and if no medical contraindication exists, thoracotomy to obtain a sample of the tumor for biopsy is indicated. If this be an "excision biopsy" so much the better.

SUMMARY

The study of the life history of cancer of the lung is best made by serial roentgenograms. The course of the disease as observed in this manner is herein described.

As a result of these studies certain facts emerge as follows:

1) Cancer of the lung has a greater duration from its inception until death than has hitherto been considered.

2) In a small series of inoperable cases the average minimum duration of life was 22.5 months.

3) In a series of operable cases the average minimum duration from the time of the first roentgen evidences until surgery was 36.4 months.

4) Roentgen findings are usually present in the pre-symptomatic stages of the disease and are almost invariably present after the onset of symptoms.

5) The earliest roentgen evidences of the disease have been recorded as long as nine years before the death of the patient and as long as four and one-half years before the onset of symptoms.

6) The extension of peripheral lesions centrally thus simulating an origin in a large bronchus is described.

7) The development of roentgen evidences of obstruction long after the appearance of an enlarged hilum shadow is traced.

8) The various roentgen signs which appear early are delineated. The most frequent and important of these is an enlargement and irregularity of one hilum shadow.

RESUMEN

La historia vital del cancer se hace mejor por la serie de roentgenogramas. El curso de la enfermedad asi observado se describe.

Come resultado de este estudio ciertos hechos emergen como sigue:

1) El cancer del pulmón tiene una duración desde su iniciación hasta la muerte, mayor de lo que hasta aqui se habia considerado.

2) En una pequeña serie de casos inoperables el mínimo-medio de duración de la vida ha sido de 22.5 meses.

3) En una serie de casos operables la duración media-mínima desde el tiempo de las primeras evidencias hasta que se realizó la cirugia fué de 36.4 meses.

4) Los hallazgos radiológicos se encuentran ya en el periodo pre-sintomático de la enfermedad y son casi invariablemente presentes después del principio de los síntomas.

5) Las evidencias radiológicas más tempranas de la enfermedad se han podido encontrar hasta nueve años antes de la muerte del enfermo y hasta cuatro años y medio antes del principio de los síntomas.

6) La extensión de lesiones periféricas hacia el centro, simulando asi un origen en los grandes bronquios se describe.

7) El desarrollo de evidencia radiológica de obstrucción mucho después de la aparición de un hilio crecido se describe.

8) Se describen los diversos signos radiológicos que aparecen temprano. El más frecuente y también el más importante es el crecimiento y la irregularidad de la sombra hiliar.

RESUME

La meilleure façon d'étudier l'histoire d'un cancer du poumon est de la lire sur des radiographies en série. Les auteurs décrivent l'évolution telle qu'elle a pu être observée par ces procédés. Certains faits semblent particulièrement importants:

1) La durée de l'évolution d'un cancer du poumon depuis son début jusqu'à la mort est plus longue qu'on l'a pensé jusqu'à présent.

2) Dans une petite quantité de cas inopérables, la durée minimum de vie fut de 22.5 mois.

3) Dans une série de cas opérables, le taux minimum de temps écoulé depuis le moment de la première constatation radiologique jusqu'à la chirurgie, fut de 36.4 mois.

4) Les constatations radiologiques sont habituellement relevées dès la phase présymptomatique de la maladie, et d'une façon à peu près constante, elles existent dès que les symptômes ont fait leur apparition.

5) Les premières constatations radiologiques de la maladie ont pu être faites jusqu'à neuf ans avant la mort du malade, et jusqu'à quatre ans et demi avant l'apparition des symptômes.

6) Les auteurs décrivent des lésions périphériques qui s'étendent vers la région centrale du thorax, simulant ainsi une tumeur dont le point de départ serait dans une grosse bronche.

7) Des signes radiologiques certains d'obstruction bronchique peuvent

apparaitre longtemps après une image qui n'était caractérisée que par des ombres hilaires augmentant de volume.

8) Les auteurs précisent les différents éléments radiologiques qui permettent un diagnostic précoce. Le plus fréquent et le plus important en est l'augmentation de volume et l'irrégularité des ombres d'un des hiles.

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A Special Complex of Pulmonary Tuberculosis in the Right Upper Lobe with Involvement of the Interlobar Pleura*

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This paper is concerned with a special complex of pulmonary tuberculosis in the right upper lobe to which hitherto little attention has been paid. The report is based on 40 cases, 20 males and 20 females. The age groups are:

10-15 years	1
15-20 years	8
20-25 years	13
25-30 years	4
30-40 years	7
40-50 years	7

The diagnosis rests on radiology and bacteriological evidence, history and clinical findings being of lesser significance. The features of the complex are: (1) the right upper lobe is affected; (2) the interlobar pleura is involved, constituting the lower boundary of the tuberculous lesion, forming a well-defined arch, mostly concave downwards, extending the whole breadth of the hemothorax; this is well illustrated by the photographs in the present paper. It will be shown later that the interlobar pleura may undergo changes during the course of the disease, especially as regards its position.

As to the radiological appearances of the tuberculosis, it is stressed that only cases are included in this series, in which the lesion is situated close to the interlobar pleura. Both pleura and lesion form the entity of the complex; other cases in which, for instance, only the subclavicular region is affected, the fissure being separated from that lesion by an apparently normal area of lung are excluded. The tuberculous lesion in the upper lobe may present itself in different ways, the main appearances of which are as follows:

a) The type of tuberculosis as such is essentially similar to the tuberculosis one is used to seeing elsewhere in the lung. It may spread over the whole upper lobe (case 1), or be restricted only to a part of it (case 2). X-ray evidence of cavitation is occasionally present (case 4). Among the 40 cases the whole upper lobe was affected in 34; in the other six only a part of the lobe was tuberculous.

b) In 12 cases the films showed a homogeneous, more or less dense opacity which occupied the whole or nearly the whole lobe, resembling an obstructive atelectasis (cases 3 and 4). Through this curtain details of the tuberculous process were often visible, at least in films taken with

*From the Chest Clinic, Hull, England.

penetration. In 11 cases of this group definite cavitation was present (cases 3 and 4). In some instances the homogeneous opacity was limited to a part of the lobe especially the periphery, adjacent to the fissure (case 2). In two cases (2 and 3) the hilum appeared to be enlarged.

Tuberculous manifestations might also exist concurrently in other parts of the lung, either on the same side or on the other, or on both sides.

Additional radiological manifestations were those of shrinkage and retraction, namely, sloping thoracic cage and retraction of the trachea and the upper mediastinum to the right. The manifestations of shrinkage do not develop in the initial, but only at some later stage of the disease.

Physical findings did not suggest the particular type of tuberculosis later revealed radiographically. Lesions occupying a large area of the lobe may produce dullness, bronchial breathing, rales or signs of cavitation, etc., but signs may be absent even in a typical advanced case. Retraction of the chest and diminished respiratory movements in the area concerned are visible on inspection corresponding to the radiological findings mentioned above.

Tuberculosis was proved in all cases by the presence of bacilli in the sputum.

The Later Clinical Course

None was given specific medical or surgical treatment but bed rest was instituted. In this way the natural course and evolution of the disease can be guaranteed. As to the subsequent course, there are two groups: the first consists of cases whose disease ended in healing; in the other group, they either remained static, or progressively deteriorated.

1) Among the 34 cases in which the whole upper lobe was affected 15 healed and 19 deteriorated. Complete healing was especially striking, where

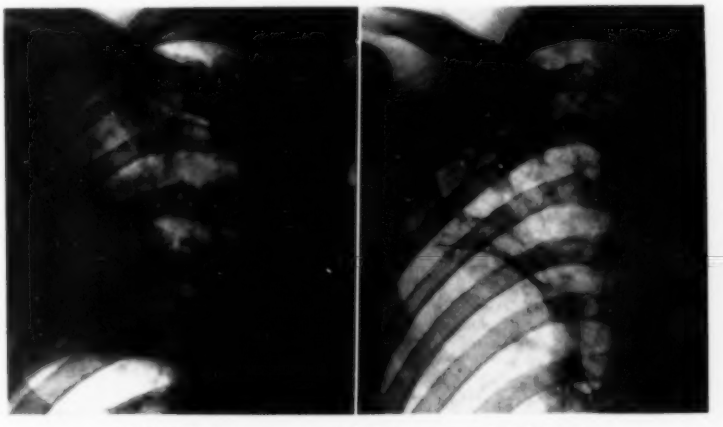

FIGURE A (CASE 1) FIGURE B

CASE 1. R.S., 23 years: *Figure A* (23.6.44): Diffuse infiltration; patchy opacity in right upper lobe, becoming more homogeneous in the outer and lower part of the lobe. The fissure runs in a horizontal, slightly curved line.—*Figure B* (11.5.46): Resolution of the lesions. Rather considerable fibrosis. The fissure lies much higher and forms a definite arch.

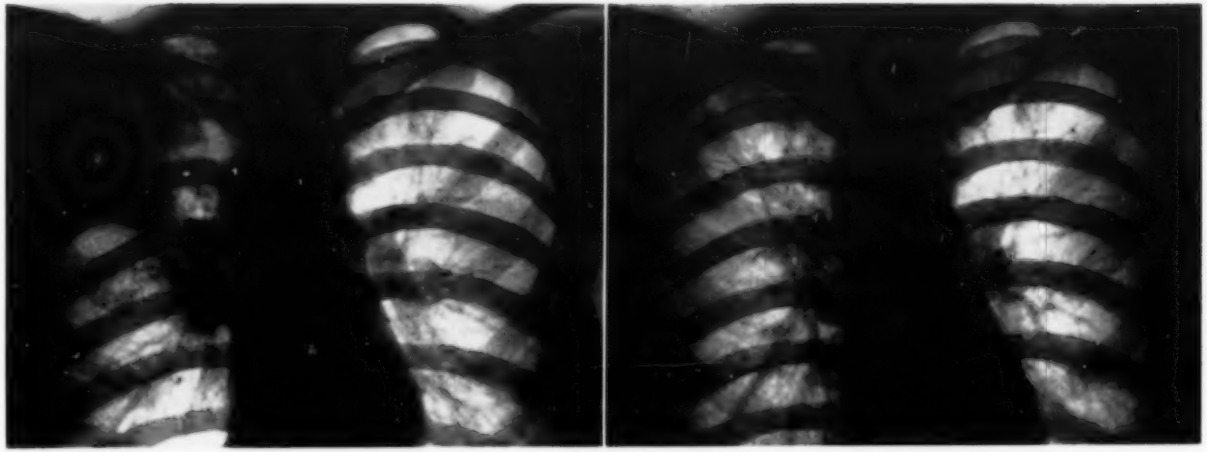

FIGURE A (CASE 2) FIGURE B

CASE 2, J.C., 24 years: *Figure A (31.7.41)*: Homogeneous triangular shadow occupying the lower outer part of the lobe. Nodular infiltration elsewhere in the lobe. Horizontal interlobar fissure. Enlargement of the hilum. Slight infiltration in R. midzone.—*Figure B* (12.10.44): The tuberculous lesions have been replaced by fibrosis. The fissure runs from the hilar area to the upper third of the first interspace. The hilar enlargement and the infiltration in R. midzone have disappeared.

extensive tuberculosis with gross cavitation had previously existed, where ordinarily one would not expect spontaneous healing.

For several reasons, a statement on the time required for healing of the individual cases has been omitted. One of the reasons is that adequate data were not available in all cases, x-ray films not having been taken often enough.

Healing took place (as seen radiologically) either by resorption and/or by calcification and/or by fibrosis and shrinkage.

Resorption can be complete or partial in combination with fibrosis (case 1). Shrinkage (case 2) manifests itself by upward displacement of the interlobar pleura. One must visualize that a normal fissure is represented radiologically by a horizontal line which forms with the right upper mediastinum an angle of about 90 degrees the vertex of which is in the hilar region (case 1). In some cases of the series the fissure changes direction, so that the angle is no longer 90 degrees, but may become 50 or 40 degrees (case 2), or even less. In pronounced cases the peripheral end of the fissure is finally situated in the middle of the apex or even still nearer to the midline. In others, the fissure seems to be slightly elevated only and/or somewhat curved upwards (case 1).

Other x-ray manifestations of shrinkage are seen including retraction of the homolateral thoracic cage and displacement of the trachea and mediastinum towards the affected side. Abnormal physical signs if present originally may persist after completion of healing, e.g. bronchial breathing, due to conducted sounds from areas in the fibrotic lung tissue.

FIGURE A (CASE 3) FIGURE B

CASE 3, M.C., 18 years: *Figure A* (15.6.45): Groundglass opacity suggestive of Atelectasis. This film was taken after a feverish illness. Two other films (8.9 and 21.9.45) showed the same manifestation. Gradual deterioration.—*Figure B* (12.9.46): Dense homogeneous opacity with several small cavities. The fissure is high and concave downwards. Patient died of Phthisis.

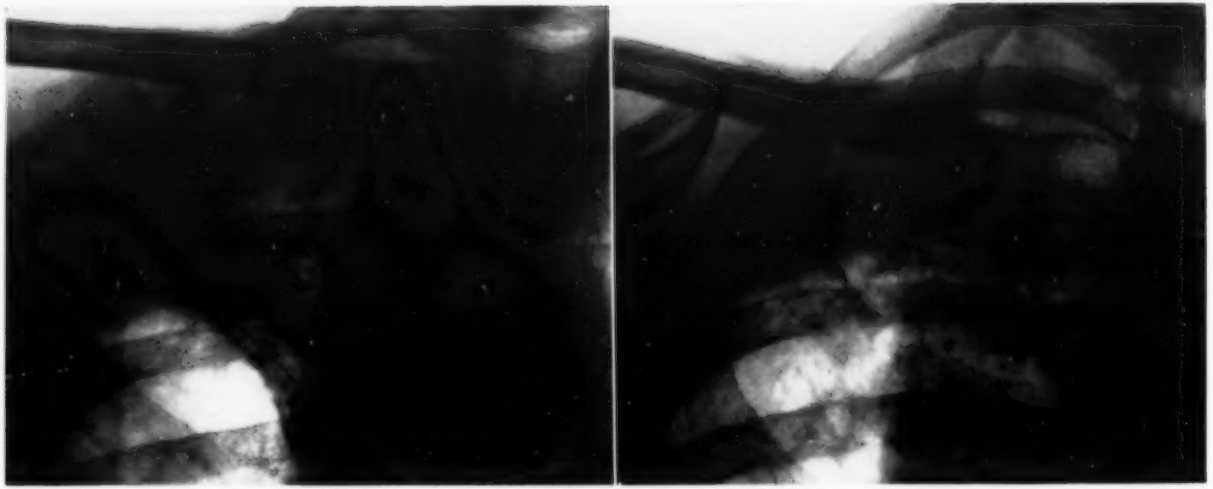

FIGURE A (CASE 4) FIGURE B

CASE 4. A.J., 35 years: *Figure A* (20.9.44): Homogeneous opacity within which a cavity is to be seen (not very distinct in the photograph). Interlobar fissure high and curved. Trachea retracted to the right. Sputum always positive. The condition had been stationary for about three years after which time the patient who had always been well and working, gained weight. The sputum became negative.—*Figure B* (19.7.50): The opacity is much smaller. Cavity and fissure are not visible any more. Trachea and upper mediastinum retracted to the right. Sputum negative.

Pathogenesis of the Complex

When both the tuberculous manifestations in the upper zone and the involvement of the interlobar pleura are already manifest on the first x-ray film, one does not know whether the interlobar pleura was initially involved.

1) In four cases, ordinary tuberculosis had become established in the upper zone and had been followed over a period in serial films until one day the characteristic involvement of the interlobar fissure was found.

2) In case 3 first the x-ray manifestation was a lobar or segmental atelectasis from which the complex subsequently evolved:

A girl, 18 years of age, developed elsewhere a febrile chest illness. X-ray film showed a ground-glass opacity in the right upper lobe suggestive of atelectasis. A radiologist diagnosed atypical pneumonia. Results of sputum tests, if they were done at that time, are not known. X-ray films taken there three months later showed no essential change.

In the following months her condition deteriorated, and was accompanied by loss of weight, cough and sputum. X-ray film taken six months later showed typical complex with several cavities. Clinically the right upper chest showed retraction, dullness, bronchial breathing and cavitation signs. Sputum contained tubercle bacilli (large numbers). The deterioration was gradual until death.

Discussion

A special type of pulmonary tuberculosis involving the right upper lobe has been observed, the features of which warrant its establishment as a separate entity. No references to it have been found in the literature with the exception of a paper by B. H. Y. T'Ang and Chien-Lang. These authors deal with the right upper interlobar pleura in general, its displacement and the part it plays in pulmonary tuberculosis, but their purpose and observations differ from mine. They mention displacement of the pleura not only upwards, but also downwards. This means that their subject is not only tuberculosis situated in the upper lobe, but also in the other parts of the lung. In some of their cases the tuberculous lesion is not delimited by the fissure, but occupies only a small area in the apical or subclavicular region. Furthermore, they include in their series cases of tuberculosis treated by artificial pneumothorax or phrenic crush. Phrenic nerve interruption may cause a considerable elevation of the diaphragm, resulting in relaxation of the lung and upwards shift of the interlobar fissure. This process is, of course, different from the displacement of the fissure by natural shrinkage. The observation described in the present paper have but little in common with those of these Chinese authors.

Several Points Require Comment:

1) The significance of the interlobar pleura. The x-ray picture is typified by involvement of the interlobar pleura which gives the impression of constituting a barrier to the advance of the disease. There is nothing, so far, to account for the often pronounced shrinkage and tendency to spontaneous healing by resorption or fibrosis and calcification. The fissure

being the lower boundary of the disease participates in the process of shrinkage in a passive, and not in an active way.

From the differential diagnostic point of view, it is important to know that similar radiological appearances as have been described can be caused by other diseases, namely typical and atypical (bacterial) pneumonia, (virus) pneumonitis, bronchial carcinoma.

The x-ray film alone is inconclusive in determining the aetiology of disease; history, signs and symptoms and bacteriological tests being essential.

2) The relation between the position of the fissure and the stage of the disease. If it is transversely directed from the mediastinum to the periphery at the level where the normal fissure is situated, shrinkage has not yet come into operation (case 1). However, it is not forseeable whether the fissure will persist in that position or not. In most cases of the series the fissure had adopted a curved position, arching upwards, as seen on the first film, a finding which indicates that shrinkage was already in operation, irrespective of whether other manifestations of shrinkage (affecting the thoracic cage, trachea, etc.) were present. The finding of an upwardly displaced or arched fissure is of some practical significance in so far as it is to some degree suggestive that further shrinkage and healing may ultimately take place.

Shrinkage of the upper lobe and displacement of the fissure can be pronounced. The angle between the fissure and the upper mediastinum may become reduced to 25 or 30 degrees or less, the vertex lying on the mediastinum at level of the hilum, one arm being the displaced fissure, the other the line of the upper mediastinum. The right upper lobe may shrink to form a triangle, the appearances then simulating an obstructive atelectasis due to bronchial occlusion by tuberculosis, tumour, foreign body or mucous plug. The tuberculous nature of the lesion is recognized by the history and by the clinical, bacteriological and radiological findings and by the knowledge of the evolution of the illness.

Secondary emphysema has not been apparent radiologically in any of the cases in spite of considerable shrinkage of the right upper lobe.

It is probable that evolution of the complex from an atelectasis as described above, has occurred in case 3.

The cause of the atelectasis is unknown, no bronchoscopy having been performed. Bronchoscopies will be done in the future, irrespective of the stage of the disease found at the initial examination. There are other possible ways of evolution as is suggested by cases in which the fissure is later involved after tuberculosis has been found in the upper zone.

Although there are no reliable signs pointing to healing, the tendency in that direction and the possibility of ultimate recovery might be expected in patients in whom the general condition is good and who remain afebrile and well and when weight is maintained when active life is resumed. Prediction in regard to a benign course or even recovery from the illness is rendered difficult. Several years may elapse before the healing process comes into operation. Owing to extraordinarily favorable circumstances an opportunity was given in several cases to follow the evolution of healing

over a period of years. In case 4, for instance, the typical complex had been present for three years without any obvious x-ray change when, for unknown reasons, healing by shrinkage was seen to be taking place and was later confirmed.

Under these variable circumstances one should not delay medical or surgical treatment either in stationary or progressive cases after a short preliminary period of conservative treatment and bedrest for three or four months, even though such an attitude may prove to be wrong as is shown by case 4, a male who had cavitary tuberculosis. This man remained well and doing a full-time job. After three years of observation, his condition was unchanged and his sputum was consistently positive, he was advised to undergo major surgical treatment. He declined because of his feeling of well-being and fitness for work. Two years later shrinkage, cavity-closure and complete healing had occurred. Less striking, but also noteworthy is case 1, in which unexpected healing started and proceeded after two years during which the condition was stationary. If the two cases had been given chemotherapy or if surgery had been done, the outcome would have been attributed to one of these measures.

The proneness to spontaneous healing is not so frequent or consistent as it is in other types of pulmonary tuberculosis described by me in 1944 and 1947, namely "localized miliary tuberculosis" (1947), and the so-called "cavitation complex" (1944 and 1947).

SUMMARY

A special complex of pulmonary tuberculosis has been described. It is exclusively situated in the right upper lobe; the lower boundary is the interlobar pleura between upper and mid-lobes.

Spontaneous healing may occur and takes place by resorption, fibrosis (shrinkage) or calcification. Corresponding to the type of healing radiologically the interlobar pleura may disappear or its position may remain unchanged or it may be displaced upward. Other cases exhibiting the complex do not show proneness to spontaneous healing; they remain stationary or deteriorate and end fatally.

RESUMEN

Una forma especial de complejo tuberculoso se describe. Se encuentra exclusivamente en el lóbulo superior derecho y el límite inferior es la cisura interlobar supero-media.

La curación espontanea puede ocurrir y se lleva a cabo por reabsorción, fibrosis (retracción) o calcificación.

De acuerdo con la forma de curación, radiológicamente la pleura interlobar puede desaparecer o su posición puede permanecer inalterada o puede desplazarse hacia arriba. Otros casos que presentan este complejo no muestran tendencia a la curación espontánea sino que permanecen estacionarios o empeoran y terminan fatalmente.

RESUME

L'auteur décrit un tableau spécial de tuberculose pulmonaire. Les lésions sont situées uniquement dans le lobe supérieur droit; la limite inférieure est la plèvre interlobaire qui sépare le lobe supérieur du lobe moyen.

La guérison spontanée est possible, et se caractérise par la résorption des lésions et un fibro-thorax (rétraction) ou par calcifications. Selon le type de guérison radiologique, on peut voir disparaitre la limite de la plèvre interlobaire, dans d'autres cas, sa situation peut rester sans modification ou elle peut être déplacée vers le haut.

Dans d'autres observations caractérisées par le même aspect, il n'y a pas tendance à la guérison spontanée, les lésions restent inchangées, ou augmentent, et finissent par entrainer la mort.

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Sidero-Silico Tuberculosis in a Foundry Employee

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Medical literature abounds with reports concerning silicosis and tuberculosis as well as combinations of the two. Instances of siderosis, siderosilicosis, and sidero-tuberculosis are on record, but the writer has been unable to find any reference to "sidero-silico-tuberculosis" in the material at hand. Undoubtedly such cases exist since there are on file numerous occupational histories of workmen who have been exposed to mixtures or concentrations of the specific dusts known to produce these respiratory afflictions. They probably have gone unrecognized because the opportunity for such complete investigation, as occurred in the present instance, did not present itself.

M. S., an adult, white male, 59 years of age, first came under observation in April, 1933. His occupational history indicates that he started working at the age of 15 as a clerk in an interurban railway office. Nine years later he took a position in a dairy bottling plant where he remained six months. In 1916 he accepted a job in the cleaning room of a manganese steel foundry where he is still employed. For 11 years he was an inspector in this department. This job which entailed some grinding could have offered intermittent exposure to free silica as well as iron oxide. He also worked in the production department for a period of one year, after which he did grinding and burning on manganese steel castings. The grinding wheels used in this plant since 1925 were composed of a resinoid bond and aluminum oxide abrasive. The following two years he worked as a burner and chipper in the same part of the plant. For the last 16 years he has been a foreman in charge of the cleaning room. As such, his duties take him to all sections of the department. Altogether he had exposure to cleaning room dust over a period of 34 years.

The cleaning room of this particular plant is a large building having an area of 35,000 square feet and a volume of approximately 1,000,000 cubic feet. Allowing for the area allotted to storage, benches, and machines, each workman has about 140 square feet of floor space. Castings which vary in weight from a few pounds to several tons are subjected to grinding, chipping or burning operations to remove fins, gate, risers, etc. These procedures produce varying amounts of dust which is composed of the abrasive material, plastic binder from the grinding wheels, adhering sand and scale, and metallic particles from the castings.

Exhaustive industrial hygiene studies were carried out in this plant over a period of 10 years, 1941 to 1951 inclusive, to determine accurately the degree of exposure to respirable sized particles of dust (below 3 microns and especially those below 1 micron in size), the components of the dust and the percentage of harmful ingredients present. As stated in a previous paper,[1] over 328 representative samples of air borne dust were collected by means of the midget impinger, electrostatic precipitator, and salicylic acid filter under summer and winter conditions of ventilation. Total dust counts ranged from 0.4 to 210 million particles per cubic foot of air, with an average of 25 million particles per cubic foot of air.

The samples were analyzed by chemical, petrographic, elutriation, and x-ray diffraction methods. Additional analyses were made to determine the percentage of free silica and iron oxide in the particle size range below 5 microns. The results

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in all samples subjected to x-ray diffraction indicated that the amount of free silica in the atmospheric dust ranged from 1.5 to 16.3 per cent, with an average of 6.2 per cent. A dust sample containing 75 per cent or even 100 per cent free silica does not necessarily represent an unsafe exposure as long as the count is of a low order of magnitude. In this instance the average count was 25 million particles per cubic foot of air which is not considered excessive for a mixed dust. Also, the count included other components as well as free silica. In other words the average total dust count was moderate and the average percentage of free silica it contained was low. The iron oxide ranged from 37.4 to 90.0 per cent, with an average of 64.3 per cent. When the iron oxide was expressed in terms of atmospheric concentration, it ranged from 14 to 224 milligrams per cubic meter of air, with an average of 49 milligrams per cubic meter of air.

The calculated values for exposure to free silica based on the dust counts together with the percentage of free silica were well below the maximal allowable concentration of 5 million particles per cubic foot of air. On the other hand, the average exposure to atmospheric iron oxide was well in excess of the highest published safe limit of 30 milligrams per cubic meter of air. It will be seen therefore that the exposure to which the employee was subjected was mainly iron oxide. Free silica was also present but only in concentrations which are not considered particularly significant.

Physical examination on August 21, 1942, disclosed a well developed man of healthy appearance, 50 years of age, 5 feet 10 inches tall, weighing 155 pounds. He had no complaint and stated that he had suffered no serious injuries, illnesses or operations. The subjective examination was negative. His temperature was 98.6 degrees F. and vision without glasses was 20/25 in each eye. Examination of the ears, nose, and throat showed no abnormality. The sinuses illuminated normally. The circumference of the chest was 34 inches at rest, 36 inches during full inspiration, and 33½ inches at full expiration. Inspection, palpation, percussion, and auscultation revealed no significant findings. The pulse rate was 76 per minute at rest, 96 after exercise and 84 two minutes later. The rhythm was regular and the quality good. Systolic blood pressure was 108 and diastolic 62. Examination of the heart disclosed no unusual changes. The remainder of the physical examination was essentially negative. The sedimentation rate showed a

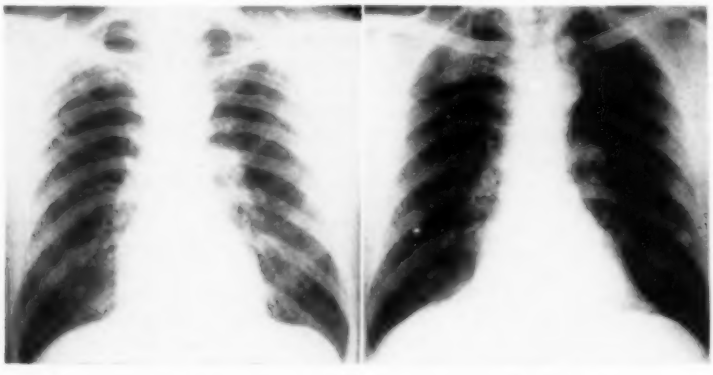

FIGURE 1 FIGURE 2

Figure 1: Roentgenogram taken in June 1934, showing early pulmonary nodulation and development of small density in first right interspace (artefact in right mid lobe area). — *Figure 2:* Film of November 1946, showing increase in size of shadow in right first interspace. The nodular pattern has not changed significantly.

maximum settling in five minutes of 1 mm. A Kahn test was negative. The specific gravity of the urine was 1030. No sugar or albumin were found.

Subsequent physical examinations in 1946, 1948, and 1949 revealed no change in the man's physical condition except a visionary defect and mild impairment of hearing. An electrocardiogram made on January 18, 1950, showed no findings of clinical significance.

The first radiograph of the chest on this employee was made on April 25, 1933. Except for some exaggeration of the linear markings of the lungs it was negative. A roentgenogram taken in June the following year showed early nodular shadows indicative of pulmonary occupational disease and the development of a small density in the right first interspace. This was classified as possible early minimal tuberculous infection. The next chest radiograph was not made until July, 1936. There was no definite change in the density in the first right interspace but the nodulation throughout the lung fields was now definite. In addition a small opacity appeared in the left first interspace. This did not seem especially serious. Subsequent x-ray films of the chest in 1942, 1943, and 1944 showed no further alteration of the lung shadows except some slight increase in the process in the right first interspace. From the year 1942 on, he was shown his chest roentgenograms and the findings were fully discussed with him. He remained completely free of symptoms which might be referable to his lungs.

Chest films made on June 15, 1946 and November 21, 1946, disclosed the fact that the density in the first right interspace was now slightly larger and appeared to involve the second interspace as well. The nodulation showed no appreciable change. At this time he was asked to come in for a consultation following which he was referred to Dr. Jerome Head[2] for further examination. Dr. Head was of the impression that the lesion was a tuberculoma although the possibility of malignancy was carefully considered. Laboratory studies including guinea pig innoculation of gastric washings were ordered but there does not appear to be any record that he reported for these. Additional films of the chest were made in March, April, May, June, and October of 1947, and in January and April of 1949. None of

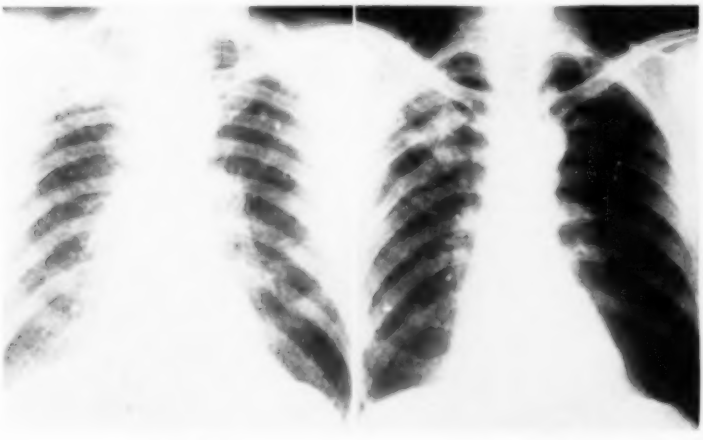

FIGURE 3 FIGURE 4

Figure 3: Chest roentgenogram made on March 3, 1950, showing further increase in size of density in right apical area. — *Figure 4:* Chest x-ray film of March 1, 1951, following resection of mass in upper right lobe. No further change in the nodular shadows previously noted.

these revealed any important change so that the possibility of neoplasm seemed remote.

In March of 1949 he was again seen by Dr. Head who thought that the lesion was now definitely a tuberculoma. Another chest roentgenogram was advised in from three to four months. This film, made in July 1949, showed no further change. On April 3, 1950, he was again examined by Dr. Head who, after reviewing the latest film of March 3, 1950, expressed the opinion that since the shadow in the upper right lung had been slowly increasing in size during the past 10 or 15 years it would eventually cause trouble. He advised surgical removal rather than await further developments.

The entire series of chest roentgenograms was also reviewed by Dr. Leonard J. Bristol[3] whose interpretations were in general agreement with our own. Dr. Bristol's opinion was that the "peculiar mottling" seen throughout both lung fields was not compatible from a roentgenological point of view with silicosis, but the probability of a benign pneumoconiosis such as siderosis should be entertained. With regard to the other roentgenographic lung changes, he commented as follows:

"The changes in the right upper third have been present since the film of June 22, 1934, and the area of involvement has increased until in the film of March 3, 1950, it measures 3 x 5 cm. in diameter. It is characterized by a homogenous increased density. Considering the length of time that this process has been present, it would seem reasonable to exclude a malignant neoplasm. However, its appearance is compatible with a tuberculoma, and in all likelihood this is what one would expect to find from histological section. Another factor in favor of this impression is the presence of a lesion in the left upper third, which is presumably the result of tuberculosis.

"In the presence of an adequate history of exposure, the presence of siderosis should be strongly considered."

On May 5, 1950, an exploratory operation of the chest was performed by Dr. Head whose operative report follows:

"Through an incision extending outward from the spine on the right the fifth and sixth ribs were cut across posteriorly and the pleural cavity was entered through a subcostal incision. There were no adhesions. The lung was extremely black. In the posterior aspect of the apex was a hard mass. This was yellowish and glistening on the surface and had the appearance of cartilage. Clamps were put about it. It was excised and the lung was closed with continuous sutures of No. 1 chromic catgut. The ribs were pegged. One pericostal suture was inserted. Two catheters were left in place for drainage. The wound was closed with interrupted silk sutures."

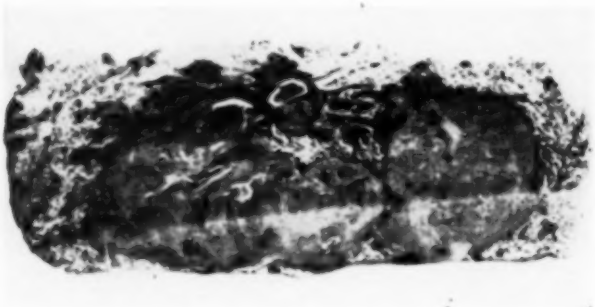

FIGURE 5: Low power photograph of a section of the lung. Note the large, lobulated area of consolidation, containing many foci of black pigment. (1.5 x).

The patient made an uneventful recovery and returned to his regular work on July 10, 1950.

The lung tissue removed at operation was sent to Dr. Arthur J. Vorwald[4] for pathological study. His report is so complete and enlightening that it is herewith quoted verbatim. The author is also greatly indebted to the Saranac Laboratory for the very excellent illustrations of the microscopic sections of the lesion appearing in this presentation.

"*Specimen of Lung:* The specimen is a block of lung tissue derived presumably from a 'wedge resection of the lesion in the right upper lobe.'

"*Gross Description:* The block of tissue measures only 2 x 2 x 1.5 cms., and its precise location in the lung is not clear, except that it is apparently from the periphery since it is lined with pleura on one side. The pleura is generally thin, but there is a plaque of dense white scarring about 2 mms. thick. On the cut surface there is noted considerable dense fibrous tissue with heavy, black pigmentation. There are a few foci of gray, soft material suggesting caseation. There is also a small amount of air-containing lung tissue, with small alveoli of uniform size.

"*Microscopic Description:* The lesion consists of a conglomerate mass of fibrous tissue with internal small and large foci of necrosis and scattered areas of parenchymal tissue in which alveolar structure persists.

"The fibrous tissue is, in general, acellular and hyalinized. Occasionally there is a recognizable nodular structure with thick bands of hyalinized tissue arranged concentrically not unlike that which characterizes the pulmonary reaction to free crystalline silica. In other areas the fibrotic tissue is irregularly dispersed and possesses no characteristic pattern or localization, except that it traverses the necrotic zones or forms collars about their periphery. Brown-black dust pigment is scattered throughout the fibrotic tissue and the necrotic substance. Elsewhere, especially in zones where parenchymal tissue still persists, the alveoli contain clustered macrophages in various stages of degeneration and laden with brown pigment, presumably iron oxide.

"With respect to the dust pigment, the amount of tissue submitted was not sufficient for chemical examination. Petrographic study of tissue, however, disclosed the presence of scattered mineral particles with an index of refraction and other characteristics which are the same as those of quartz.

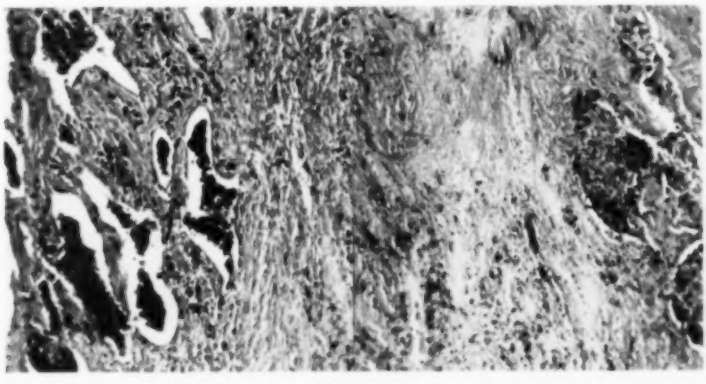

FIGURE 6: A composite photomicrograph showing at the left distorted alveoli filled with pigment-laden phagocytic cells; in the center, a wide zone of scar tissue with scattered phagocytic cells; and at the right, an area of tuberculous caseation in which the outlines of the preceding scar tissue are well preserved. The foci of pigment at the right were in phagocytic cells which are now necrotic. (100 x).

"Necrosis constitutes a prominent part of the lesion. The necrosis is caseous in type, not unlike that resulting from tuberculous infection. Occasionally the necrosis has undergone partial liquefaction and there is a rare small excavation. Some of the excavations are surrounded by a seminecrotic membrane and cellular wall somewhat resembling cavities of tuberculosis. In addition, there are occasional proliferative tubercles, some with giant cells of the Langhans' type. These are often most prominent in the peribronchiolar zones of chronic inflammation.

"The less involved parenchymal tissue immediately about the fibrocaseous mass contains occasional small proliferative tubercles, some of which tend to coalesce. Here the alveolar walls are thickened, presumably the result of extension of the tuberculous process. The alveoli are filled with macrophages loaded with brown pigment.

"The parenchymal tissue further removed from the main mass also contains scattered macrophages laden with brown pigment, and the adjacent alveoli are sometimes filled with such cells. Although the alveolar walls and alveoli are considerably distorted, yet the walls are only slightly thickened and there is frequently little or no apparent inflammatory reaction to the pigment, which is presumably iron oxide. Some of the vascular trunks are thickened, but this is a common finding in tissue neighboring an active tuberculous process such as described.

"Some of the bronchi and bronchioles exhibit wide proliferation of their epithelial mucosa. There is no evidence of malignancy.

"*Comment:* The case is an extremely interesting one because of the single focal fibrocaseous lesion which resulted apparently from the combined action of a fibrogenic dust and a tuberculous infection. The histological character of the fibrosis supported by the petrographic findings and the occupational history of exposure to free silica indicate that the dust is siliceous in type. The fibrosis is not typical for classical silicosis in that it fails to demonstrate the degree of hyalinization and the configuration and nodulation usually discovered in so-called conglomerate lesions of the disease. Therefore it would appear that the amount of silica deposited in the lesion was indeed small, yet sufficient to stimulate a fibrotic response in an aera harboring an active tuberculous process. However, the amount of free crystalline silica deposited in the small portion of the lung external to the

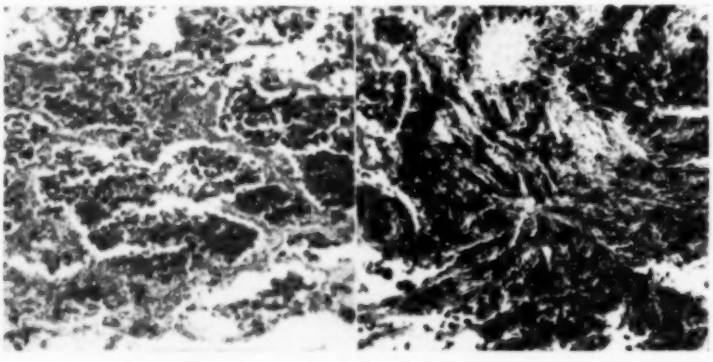

FIGURE 7 FIGURE 8

Figure 7: A focus of dust localization with a slight tissue reaction as revealed by cellular infiltration and slight thickening of alveolar walls. (100 x).—*Figure 8:* A focus of dust localization with a distinct fibrous reaction in the form of radiating strands and with obliteration of pulmonary architecture.

lesion apparently was not of sufficient magnitude to produce demonstrable silicotic reaction. If, then, this small portion is representative of the entire lung, there is every reason to suspect that silicosis is not present elsewhere. Thus, the mottled shadows seen roentgenographically are in all probability the result of a benign pneumoconiosis such as siderosis. This interpretation is supported by the presence of masses of brown pigment, presumably iron oxide, in the small amount of parenchymal tissue removed surgically with the lesion. It is further supported by the fact that that pigment has occasioned only a very mild inflammatory response such as seen experimentally in animals inhaling iron oxide and in the lungs of a case with siderosis studied at this laboratory.

"The focal lesion of sidero-silico-tuberculosis (to be exact) without silicotic reaction elsewhere in the lung is an unusual finding in pneumoconiosis. We have studied at least one other similar case in which a whole surgical lobe of the lung was involved. Here, too, infection was present. The mechanism whereby such focal lesions arise is not fully established. It appears that the infectious process interferes with the drainage of the lung, thus allowing the local accumulation of more dust there than elsewhere in the lung where such drainage is not impaired. Also, the infectious process may modify the tissue reaction to free crystalline silica, and vice versa, and thus produce a localized combined effect which does not occur in other portions of the lung free of tuberculosis or other infection.

"In summary, the case presents a focal lesion of sidero-silico-tuberculosis with siderosis in the adjacent pulmonary parenchyma. From the tissue available it is hazardous to state categorically that silicosis is not present in the rest of the lung, but the evidence available suggests that this may be the case. In all probability the mottled shadows seen roentgenographically are due to deposits of iron oxide and therefore the presence of siderosis must be entertained."

Discussion

More than a year has elapsed since M. H. returned to work. He has lost no time during this period and states that he has no complaint other than an occasional slight cough and shortness of breath. He appears well. A routine physical examination on March 13, 1951, revealed only the minor defects previously noted with some decreased breath sounds in the right side of the chest posteriorly.

The author has observed nine similar cases in workers whose occupational exposure to dust has been of the kind described here. One of these individuals developed a large cavity in the upper right lobe, but a concentrated sputum test and guinea pig innoculation of gastric washings failed to disclose the presence of tubercle bacilli. The other eight employees have shown no significant change in their chest x-ray films over the last 10 years.

The differential diagnosis of pulmonary lesions of this type presents a challenge to roentgenologists, chest physicians, and industrial medical practitioners. A workman's first impulse is to associate illness with his occupation and the physician is sometimes guilty of abetting or even instigating this conclusion. It offers a convenient explanation of an otherwise difficult diagnostic problem and may seem expedient since the patient is convinced of its connection with his work and desires to be so informed. Conscientious reflection however, will demand that localized shadows observed in the chest roentgenograms of the industrially employed must be differentiated from those produced by tuberculosis, sarcoid, neoplasm,

benign adenoma, mycotic disease, pulmonary cyst, infarct, atypical pneumonia, and numerous other afflications of the lungs common to people in other walks of life. One should therefore not be too hasty in designating an illness as occupational until all the facts have been considered. Careful evaluation of the data involved will include a precise history of past and present employment, complete physical examination, and serial roentgenograms of the chest. Clinical laboratory studies comprising the blood sedimentation rate, concentrated sputum analyses, guinea pig innoculations, skin sensitivity, and pulmonary function tests are essential as is also the estimation of hazardous exposure in the working environment. The latter means accurate analysis of representative samples of air borne dust collected at the breathing level of the worker to determine the character and degree of atmospheric contamination. It involves the defensive mechanism of the upper respiratory tract and its capacity to eliminate particles of dust of respirable size. The duration and constancy of exposure ought to be considered along with an appraisal of the exhaust ventilation facilities in the plant and the factor of individual susceptibility should not be overlooked.

SUMMARY

Clinical, roentgenological, and pathological findings together with industrial hygiene studies demonstrating exposure to dust in a foundry employee afflicted with sidero-silico-tuberculosis, are presented.

The data show the need for accurate appraisal of abnormal shadows in the chest roentgenograms of industrial workers in such environments in contrast to those of individuals in other walks of life.

The findings also demonstrate the value of exploratory surgical intervention in conjunction with other recognized procedures in establishing a precise diagnosis.

RESUMEN

Se presentan los estudios clínicos, roentgenológicos y patológicos, junto con los estudios de higiene industrial que demuestran la exposición al polvo, en un empleado de una fábrica de fundición afectado de sidero-silico-tuberculosis.

Los datos presentados demuestran la necesidad de avaluar adecuadamente las sombras anormales en roentgenogramas torácicos de trabajadores industriales en esos ambientes, en contraste a los de individuos en otras ocupaciones.

Los hallazgos demuestran también el valor de la intervención quirúrgica exploratoria junto con los otros procedimientos reconocidos para hacer el diagnóstico preciso.

RESUME

L'auteur rapporte l'ensemble de ses constatations cliniques, radiologiques et anatomo-pathologiques, chez des individus qui ont été atteints de sidéro-silico-tuberculose, après avoir été exposés aux poussières d'une fonderie.

Les investigations montrent la nécessité d'apprécier d'une façon précise l'existence d'ombres anormales sur la radiographie pulmonaire des travailleurs industriels, exposés au risque, en l'opposant à l'aspect radiographique des autres individus.

Il démontre également l'importance de l'intervention chirurgicale exploratrice associée aux autres procédés connus pour établir avec précision le diagnostic.

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Failure of P-(di-n-propylsulfamyl)-Benzoic Acid ("Benemid") to Influence P-Aminosalicylic Acid Blood Levels†

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It is now well established that p-aminosalicylic acid is a valuable adjunct in the treatment of tuberculosis, by virtue of both its tuberculostatic effect and its ability to prevent or delay the emergence of streptomycin-resistant strains of tubercle bacilli. Its major disadvantage lies in the fact that it is a gastrointestinal irritant and therefore cannot be given in sufficiently high dosage for optimal therapeutic effect. Efforts have been made to surmount this obstacle by several methods, namely parenteral and rectal administration, which are impractical, and the concomitant administration of compounds which might be expected to enhance PAS blood levels when the latter drug is given in small oral dosage.

In April 1950, there appeared evidence[1] that a benzoic acid derivative, p-(di-n-propylsulfamyl)-benzoic acid,†† was capable of producing a two-to-eight-fold enhancement of plasma concentrations of PAS for periods as long as eight hours. This was followed in rapid succession by two other communications[2,3] reporting substantially the same results. Since, in our estimation, these findings required independent corroboration, we embarked on a study of similar nature, the results of which are presented below.

Material and Methods

Ten patients were chosen at random from the hospital population. All were adults, and none received oral or parenteral medication of any kind during the investigation. Three types of experiments were conducted:

(a) Each patient received a single dose of sodium p-aminosalicylate, 4.0 Gm.

(b) At a later date, each patient received a single dose of sodium p-aminosalicylate, 4.0 Gm., together with a single dose of "Benemid,"††† 2.0 Gm.

(c) At a still later date, each patient received "Benemid," 0.5 Gm. every six hours for 48 hours. After the fourth dose, i.e., 24 hours after medication was begun, each patient was given a single dose of sodium p-aminosalicylate, 4.0 Gm.

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†††We are indebted to Dr. S. C. Strickland, Medical Department, Sharp & Dohme, for making available to us generous supplies of "Benemid" for this study.

All doses of sodium p-aminosalicylate were given with the patient in the fasting state and no food was allowed until two hours following the administration of the drug.

Samples of venous blood were withdrawn at 0, ½, 2, 4, 6, 8, 14, and 24 hours after the administration of sodium p-aminosalicylate, and PAS blood levels were estimated by the method of Street.[4] To demonstrate the reliability of this method, several technical controls were employed, as follows:

(1) A series of tests was run on the blood of a patient who had received a single dose of "Benemid," 2.0 Gm. (without sodium p-aminosalicylate). The values were consistently zero.

(2) In certain instances it was necessary to refrigerate blood specimens for periods of varying duration. In order to ascertain whether such periods of refrigeration would influence PAS blood levels, a series of duplicate tests was run on freshly drawn blood and on blood which had been refrigerated for 24 and 48 hours. There was no variation in the results obtained.

(3) Each set of estimations was accompanied by a reagent "blank," performed on a 10 mg. standard. This gave consistent results.

(4) Each day's set of estimations was accompanied by a comparison with the previous day's peak specimen.

Results

Table I illustrates the average PAS blood levels of the 10 patients in each of the three experiments described above. Figure 1 is a graph derived by plotting the average PAS blood levels of the 10 patients in each experiment against the times at which blood samples were taken. The following characteristics are to be noted:

(1) In all cases, there is a sharp rise of blood PAS levels in the first half hour.

(2) Blood levels fall precipitously between two and four hours, and then more gradually until zero or near-zero levels are reached at eight hours.

TABLE I: Comparison of Blood Para-aminosalicylic Acid Levels Before and After the Oral Administration of p-(di-n-propylsulfamyl)-Benzoic Acid (Benemid) (Averages of 10 Patients).

(Values Represent mg. PAS per 100 ml. Whole Blood)

	PAS Alone	PAS with Single Dose Benemid	PAS with Multiple Dose Benemid
½ hour	3.5	3.0	3.6
2 hours	4.1	4.2	4.3
4 hours	1.1	1.7	1.8
6 hours	.36	.59	.48
8 hours	0	.12	.12
14 hours	0	0	0
24 hours	0	0	0

(3) *No significant differences in PAS blood levels are demonstrated whether sodium p-aminosalicylate is given alone or together with single or multiple doses of "Benemid."*

Although, for the sake of brevity, we have averaged the results in the three groups of experiments, we would stress that, in no individual case was a significant enhancement of blood level noted.

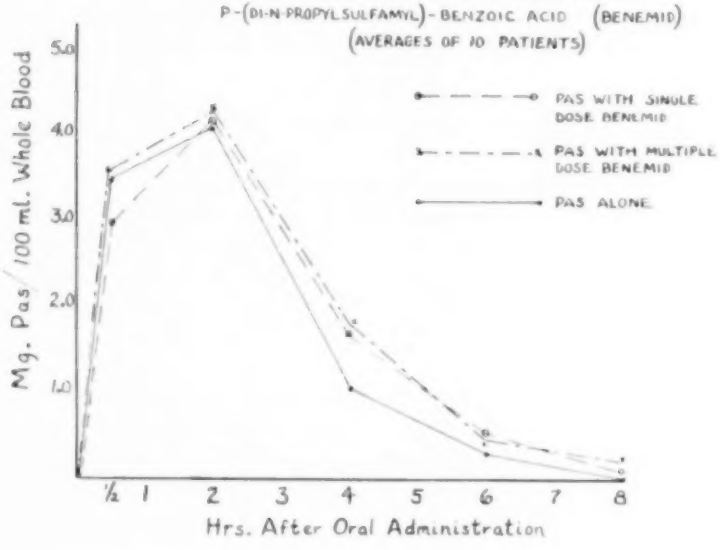
During the course of the study it was noted that four of the 10 patients complained of gastric distress, ranging from mild heartburn to actual nausea and vomiting. These symptoms were not present when sodium p-aminosalicylate alone was given, but were complained of exclusively following the oral administration of "Benemid."

Discussion

It is obvious, from these results, that we were unable to demonstrate any significant enhancement of PAS blood levels by the concomitant administration of "Benemid." It will be noted, in substantiation of these findings, that other workers,[5,6] have obtained similar results. It may be argued that, since we have employed a different method for the determination of blood PAS concentrations from that used by the original workers, the results are not susceptible of comparison. We would point out, however, that our study was originally begun using a similar chemical method to that employed by Boger et al.[1] but that, in our hands, the results were so inconsistent that the method was abandoned in favor of the present one. Furthermore, in view of the number and character of the technical controls as outlined

FIGURE 1.

COMPARISON OF BLOOD PARA-AMINOSALICYLIC ACID LEVELS BEFORE AND AFTER THE ORAL ADMINISTRATION OF P-(DI-N PROPYLSULFAMYL)-BENZOIC ACID (BENEMID) (AVERAGES OF 10 PATIENTS)



under "Material and Methods," we are satisfied that this method is a reliable one.

It seems clear, therefore, that no advantage is to be gained by the addition of "Benemid" to PAS regimens in the treatment of tuberculosis.

SUMMARY

1) P-(di-n-propylsulfamyl)-benzoic acid ("Benemid"—Sharp & Dohme) was administered orally to 10 patients in conjunction with sodium p-aminosalicylate, and PAS blood levels were determined at specified intervals for 24 hours.

2) No significant enhancement of PAS blood levels was noted.

3) It is concluded that no advantage is to be derived from the concomitant administration of "Benemid" with sodium p-aminosalicylate in the treatment of tuberculosis.

RESUMEN

1) El p-(di-n-propylsufamyl)-acido benzoico (Benemid de Sharp & Dohme) fue administrado por via oral a 10 enfermos al mismo tiempo que el paraminosalicilato de sodio y los niveles de PAS fueron determinados a intervalos especificados durante 24 horas.

2) No se noto sostenimiento alguno del tenor de PAS en la sangre.

3) Se concluye que no se obtiene ventaja alguna del uso concomitante de Benemid con el paraminosalicilato de sodio en el tratamiento de la tuberculosis.

RESUME

1) Du p-(di-n-propylsulfamyl)-d'acide benzoique ("Bénémid"—Sharp & Dohme) a été administré par voie bucale à dix malades, en association avec du p-amino-salicylate de soude. La quantité de PAS sanguine a été déterminée à intervalles fixes pendant 24 heures.

2) On ne put constater une augmentation notable du taux du PAS sanguin.

3) La conclusion de ce travail est qu'il n'y a aucun avantage à associer au PAS de soude le "Bénémid" dans le traitement de la tuberculose.

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Tibione (Amithiozone) in Pulmonary Tuberculosis*

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In this paper we shall present the early evolution of 96 cases of pulmonary tuberculosis treated with "Tibione" (amithiozone), of whom 49 were men and 47 women ranging in age from 13 to 60 years. The majority of the patients were from 15 to 40 years old.

Classification of these patients was as follows: two minimal, 52 moderately advanced, among whom were 28 with cavities, and 42 far advanced cases, including 37 with cavities. Many of these patients had been previously treated with other antibiotics or other forms of chemotherapy (streptomycin or PAS), without control of the lesions being effected. In order to avoid the possibility of a late reaction from previous treatment, all those who had not passed a minimum period of two months without treatments were rejected. The results obtained with the earlier treatment had been poor. Of the 96, only 22 had not been treated, these being almost all evolutionary cases. Of the 74 who had received some kind of drug, only 11 had shown slight improvement and the rest either remained the same or continued getting worse.

We began to administer Tibione in small doses of 0.025 grams during seven days, increasing the dose weekly in 0.025 grams until we reached a maximum daily dose of 150 mgrs. We thought that in this way we would avoid, in great part, the appearance of toxic symptoms. The total dose received by our patients was from 5 grams minimum to 32 grams maximum, during two to ten months.

In detailing the results obtained we will refer in the first place to the effect on general condition, symptoms such as cough, expectoration and fever, weight, bacillus and sedimentation rates, leaving for the end our observations in regard to the pulmonary lesions.

The general condition of the majority of the patients improved considerably. Fifty-six of the patients had presented an aspect that was frankly bad. Of these, 36 were improved.

Eighty-three per cent of all cases had temperature elevation before treatment was begun and the drug administered. This percentage went down progressively: at the 5 gram stage, only 67 per cent had fever; at the 10 gram phase only 34 per cent; and at 20 grams the percentage had gone down to 11 per cent. Therefore, as the total dose of the drug was increased the percentage of patients with fever decreased.

*In this article references are made to "Tibione" which is the registered trade mark of Schenley Laboratories, Inc., designating exclusively its brand of amithiozone. Amithiozone is the generic name (approved by the Council on Medicine and Pharmacy of the American Medical Association) of the thiosemicarbazones used in the treatment of tuberculosis and referred to in this article.

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Cough and expectoration were also favorably influenced by the drug. The weight curve also showed a marked ascent, 61 patients gained a minimum of 5 kilos.

Of our 96 patients, 86 had tubercle bacilli in the sputum when treatment was begun. At the end of the observation period 21 had negative sputum.

The erythrocyte sedimentation rate became normal in five of 53 cases where it had been 30 mm. Of the same 53 cases, 28 showed reduction and 20 were not influenced. Of the 32 cases who began the treatment with moderately accelerated sedimentation (less than 30 mm.) only seven showed improvement.

Concerning results obtained with pulmonary lesions we shall separate our findings into three groups, corresponding to the extent of lesions.

In the minimal forms, of which there were only two, a good result was obtained in one and the other was not influenced.

Of the 52 moderately advanced cases, x-ray findings showed three to be without lesions, 10 with marked improvement, 24 partial improvement, 11 showed no change and four became worse.

Among the 42 far advanced cases there was none in which x-ray shadows disappeared. Eight achieved marked improvement, 16 partial improvement, 10 were not influenced, and eight became worse.

From the anatomic-radiologic aspect, as in preceding studies, we divided our cases into those with isolated nodules, dense confluent type, and dense confluent nodules. Of the total of 23 with isolated nodules, one showed complete recovery, five marked improvement, 11 partial improvement, four were not influenced and two became worse. Of the 29 dense confluent forms, we obtained one complete result, six marked improvements, 12 partial improvements, seven without change and three that became worse. Of the 42 with dense confluent nodular forms, only one showed an excellent result and seven marked improvement, 17 partial improvement, 10 were without change and seven became worse.

Without considering either the anatomic-radiological or the lesion extension aspects, we have observed four recoveries (4.1 per cent); 18 marked improvements (18.7 per cent); 40 partial improvements (41.6 per cent); 22 unchanged (22.9 per cent); and 12 worse (12.5 per cent).

We have divided cavities into three groups according to size: (1) those of 2 cm. or less; (2) those from 2 to 4 cm.; and (3) those more than 4 cm. in diameter. In the first group (up to 2 cm.) and composed of 13 cases, there were no closures, four showed reduction, eight were unchanged, and one increased. In the medium diameter group (2 to 4 cm.) with a total of 27 cases, there were no closures, 10 showed reduction; 12 remained unchanged; and five increased. In the large diameter group (over 4 cm.) with 25 cases, there were no closures. Seven showed reduction, 15 no change and three increased.

Therefore, we may conclude that none of the 65 cases with cavities were influenced by Tibione in such a way as to obtain the formation of scar tissue. Only 21 (32.2 per cent) showed any improvement whatsoever, of the

remaining 44, 35 (54.5 per cent) showed no change and nine (13.3 per cent) became worse.

As a mere illustration, and without any intention of drawing conclusions, we should also like to point out that we had 11 cases of laryngeal tuberculosis and 11 with localized tracheobronchitic infections. In both of these groups we obtained three excellent results and eight failures. It should also be noted that all of these cases had been previously treated, at least two months before, with streptomycin and without improvement being observed.

Regarding toxicity, the most common symptom is lack of appetite, as observed in 18 of our patients. When this symptom presents itself early, it is necessary to suspend the treatment. In eight patients this symptom occurred before three grams were reached and was so intense and permanent that it was necessary to interrupt the treatment. In the remaining 10, the onset was sufficiently tardy that treatment could be maintained by a diminution in the dose.

Other signs of intolerance were: jaundice (four cases), one showing up at 5 grams and the other three around 20 grams; anemias (five cases), of whom two were of the hemolitic type and three were hipocromes; vague dyspeptic symptoms (three cases), in whom the dominant note was meterism and acidity; and finally one case of intense diarrhea which appeared at approximately 10 grams.

We looked for possible renal damage by testing the urine for albumin. In these cases a small amount of albumin was found but disappeared without suspending treatment. One patient showed much and persistent albumin in the urine and it was necessary to suspend treatment.

SUMMARY

From these observations we believe that Tibione has some use in the treatment of pulmonary tuberculosis, especially in early and spreading lesions. However, it is not comparable with streptomycin or PAS, which have shown greater activity against tuberculous focci. However, studying the results obtained in our observations we believe that aid which may be obtained with Tibione should not be disregarded.

Its general action on subjective symptomology, weight curve, sedimentation rate, etc., can be considered as sufficiently satisfactory.

Bacillus activity was, in reality, little influenced among our 86 positive cases; only 21 were converted. This result, together with our earlier work with streptomycin emphasizes that chemotherapy to date is only an aid in the treatment of pulmonary tuberculosis.

We should, under no circumstance, postpone administration of classical methods of medical and surgical treatment.

RESUMEN

Creemos, por estas observaciones, que la droga Tibione tiene algún empleo en la tuberculosis pulmonar especialmente en las lesiones tempranas y diseminadas. Sin embargo, no es comparable con la estreptomicina o el

PAS que han mostrado mayor actividad sobre los focos tuberculosos. A pesar de esto, estudiando los resultados obtenidos segun nuestras observaciones, creemos que la ayuda que pude obtenerse por el uso del Tibione no debe desdeñarse.

Su acción general sobre los signos subjetivos, curva de peso, sedimentación globular, etc., pueden considerarse como suficientemente satisfactorios.

La actividad bacilar en realidad fue influenciada poco entre nuestros 86 casos positivos; solo 21 viraron a negativos. Este resultado así como nuestros trabajos anteriores sobre la estreptomicina hacen resaltar que la quimioterapia de ahora es solo un ayudante en el tratamiento de la tuberculosis pulmonar.

Bajo ningunas circunstancias debemos posponer la aplicación de los procedimientos clasicos médicos o quirúrgicos de tratamiento.

RESUME

A la suite de leurs observations, les auteurs pensent que la thiosémicarbazone a une certaine place dans le traitement de la tuberculose pulmonaire, spécialement dans les lésions jeunes ou dans les ensemencements. Toutefois, ce produit ne se compare pas avec la streptomycine ou le P.A.S. qui ont montré une activité plus grande dans les lésions tuberculeuses. Les auteurs, en étudiant les résultats obtenus dans leurs observations pensent cependant qu'il ne faut pas trop sous-estimer l'action auxiliaire de la thiosémicarbazone.

L'action générale sur les symptômes fonctionnels; sur la courbe de poids, et la vitesse de sédimentation parait assez satisfaisante.

L'expectoration bacillifère fut en réalité très peu influencée. Sur 86 cas avec expectoration positive, 21 seulement perdirent les bacilles de leurs crachats. Ce résultat, associé aux conclusions des travaux antérieurs que les auteurs ont consacrés à la streptomycine, montre qu'actuellement la chimiothérapie n'est qu'une aide dans le traitement de la tuberculose pulmonaire.

En aucun cas, on ne doit éliminer les méthodes chirurgicales ou médicales classiques.

The Selection of Patients with Cardio-pulmonary Diseases for Air Travel*

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Patients with heart and lung diseases who have traveled long distances to hospitals for treatment, sometimes inquire if they may return home by airplane. They may express timidity or uncertainty because of a patient or friend who had become seriously air-sick and generally disturbed. Close questioning usually discloses the incident as completely inconsequential. In doubting the safety of air travel, patients may not be aware of the remarkable record of the Air Transport Command in transporting countless injured and sick during World War II and the present action in Korea. However, the questions are pertinent and considerable responsibility is placed on attending physicians to give correct and timely advice, especially in cases with possible contraindications for flying.

The basic reasons for anxiety are the fear of a lung complication or a heart attack. In order to throw light on the hazards and safety for cardio-pulmonary cases, a group of patients has been surveyed to determine the incidence of untoward effects. During the past two and a half years, 28 patients from various parts of the United States were examined and treated privately or hospitalized at the Woman's Medical College. Their diseases were as follows: pulmonary emphysema, etiology unknown, nine cases; emphysema associated with silicosis, six cases; pulmonary fibrosis due to long-standing disease such as tuberculosis, six cases; spontaneous pneumothorax (cured), three cases; spontaneous pneumothorax, three cases; pulmonary neoplasm, one case; and failure of the right heart in association with emphysema (as noted above), four cases. The destinations for travel included Florida, Missouri, Illinois, western Pennsylvania, California, Wisconsin, Ohio and West Virginia. After completing the studies the patients were advised to travel in pressurized airplanes and given letters to the air hostess indicating the diagnosis and treatment in case of emergency.

Of this group, 25 arrived safely and comfortably. The following patients left the airplane because of sickness: One patient with spontaneous pneumothorax, one case of emphysema with failure of the right side of the heart, and one with emphysema who developed marked distension of the stomach with vomiting and dehydration. All were treated by local physicians and travel was resumed by land. Correspondence indicated there was no actual emergency, although the possibility of increased intrapleural

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Abstract of a paper read at a medical meeting of the "Flying Congress," in flight on stratocruiser El Presidente, Pan American World Airways, at an altitude of 18,000 feet, on August 21, 1952, en route to the Second International Congress on Diseases of the Chest, Rio de Janeiro, August 28-30, 1952.

pressure in the spontaneous pneumothorax case and the manifestations suggesting oxygen-lack in the other patients were sufficiently important for them to receive every benefit of the doubt in treatment. It is significant to point out that the pneumothorax case traveled unexpectedly part distance in a non-pressurized airplane.

The following cases of advanced pulmonary emphysema will illustrate the safety of air travel:

R.H., age 63 years, industrialist from California, with a marked increase of residual air in the lungs (55.8 per cent of total lung volume), low oxygen saturation of the arterial blood (93 per cent), and reduced maximal breathing capacity (78.1 per cent based on predicted figure), travels extensively by pressurized airplanes. While at home and abroad he is under treatment with intermittent positive pressure (oxygen) breathing and takes the apparatus with him on airplanes for emergency use. He has suffered no untoward effects, not even when crossing the Andes Mountains.

H.T., age 64 years, industrialist from Wisconsin, is affected with severe emphysema, the tests indicating a high content of residual air in the lungs (54.7 per cent of total lung volume), decreased arterial oxygen (92 per cent) and reduced vital capacity (41 per cent decrease from predicted figure). He travels extensively by pressurized airplanes with no difficulty.

The basic disturbances of air travel relate to motion sickness and the physiological effects of increased barometric pressure, especially while passing through undulating air to altitudes of 10,000 feet or more. There are marked individual differences in the response to both conditions; i.e., some persons are remarkably free from manifestations, while a few are extremely susceptible. With motion sickness, the dizziness and unsteadiness with gastrointestinal symptoms may result from vistibular disturbances, while in altitude sickness, oxygen-lack or anoxia is the chief cause, as manifested by dyspnea, wakefulness, nervousness, anxiety, palpitation, prostration, and in severe cases gas on the stomach with nausea and vomiting. It is interesting that aging persons enjoy a remarkable freedom from the symptoms of anoxia, both on the ground and in airplanes, due in part to the adaptability of their collateral circulation acquired through the years. In pressurized cabins, even at altitudes of 10,000 feet or more, the pressure within the plane is reduced to a mere 3,000 to 5,000 feet, and any tendency to anoxia is minimized. Serious oxygen-lack may be expected in emphysema with extreme mixing and dilution problems of the lung and in pneumothorax cases when the intrapleural pressure is excessive, the heart displaced to the opposite side and the burden of breathing is left to the opposite lung.

Referring especially to the behavior of gas on the stomach and intestines while flying, it should be mentioned that gas increases in volume proportionally to the reduction of barometric pressure as the higher altitudes are reached. However, with modern air transportation employing pressurized cabins, the expansion of gas in the stomach is negligible; more often its occurrence is precipitated by air swallowing, salivation, and loosening the belt to permit abdominal relaxation. Prolonged or repeated vomiting,

with depletion of the fluid reserves of the body, is closely associated with fatigue, anxiety, and over-eating before flight time, accentuated by high temperatures or limited ventilation, especially when the plane jostles or ascends rapidly. Vistibular disturbances of the ear, once a frequent problem in the lighter aircraft of the 1930's, is extremely uncommon today. The occurrence of hemoptysis has not been noted in the present series.

Recommendations for patients with cardio-pulmonary disease are as follows:

1) Travel should be in pressurized cabins only.

2) Patients with manifest coronary insufficiency; extreme hypertension; cystic disease of the lung; recent hemoptysis; excessive cough, especially with expectoration; and recent or recurrent spontaneous pneumothorax should be advised against air travel.

3) With artificial pneumothorax cases, the pressure of the pleural cavity before flight time should be reduced to the range of -1 and $+3$ mm. Hg.

4) In cases of dilatation of the right side of the heart associated with advanced emphysema, air transportation should not be advised unless oxygen inhalation apparatus is readily available.

5) It is advisable for patients with a flabby and relaxed abdomen to wear a soft, pliable support in order to avoid undue relaxation of the abdominal wall and its contents.

6) Flight should be delayed in cases of acute sinusitis, chest colds and acute exacerbations of chronic pulmonary disease.

7) Patients who are susceptible to motion sickness should be given a prescription for an antihistaminic drug.

8) A letter should be written for the air hostess to read if/when medical problems require attention.

Patients should receive the following instructions:

1) Avoid over-eating and the use of alcohol 24 hours before flight time.
2) Obtain ample sleep and rest before the flight.
3) Don't board the airplane nervous and fatigued.
4) Don't chew gum incessantly to fill the stomach with gas and saliva.
5) Don't loosen the belt or girdle to permit the abdomen to relax and distend.
6) Don't slump down in the chair to encourage inadequate movement of the lungs.
7) Eat sparingly during flight.
8) Consult the airplane hostess if squeamishness or shortness of breath occur.

SUMMARY

The transportation by air of patients with cardio-pulmonary disease is satisfactory and usually agreeable, providing the distance is sufficient to justify the long trip to and from airports. In any event, traveling should be in pressurized cabins only, since the higher barometric pressure of the ordinary types may cause symptoms of oxygen-lack. The contraindications to air travel are cystic disease of the lung, recurrent spontaneous pneu-

mothorax, high pressure artificial pneumothorax, acute upper respiratory tract infections with exacerbations of chronic lung disease, manifest coronary insufficiency, failure of the right side of the heart, and recent hemoptysis.

RESUMEN

El transporte aereo de enfermos cardio-respiratorios es satisfactorio y generalmente agradable siempre que la distancia justifique el translado a los aeropuertos que requiere a veces largo tiempo. El viaje debe hacerse solo en aviones con presión compensada puesto que la presión barométrica aumentada en los aviones corrientes no equipados así, pueden producir sintomas de escasez de oxígeno. Las contraindicaciones para el viaje en avión son la enfermedad cistica del pulmón, neumotorax espontáneo recurrente, neumotorax artificial hipertensivo, infecciones agudas del tracto respiratorio superior con exacerbaciones en la enfermedad pulmonar crónica, insuficiencia coronaria manifiesta, insuficiencia cardiaca derecha y hemoptisis reciente.

RESUME

Le transport par voie aérienne de malades atteints d'affections cardio-pulmonaires donne toute satisfaction et est habituellement agréable si la durée du voyage est suffisante pour justifier la longueur du parcours jusqu'à l'aéroport à l'aller et au retour. En tout cas, ce n'est que dans des avions pressurisés que le voyage doit s'effectuer, de crainte que les modifications de la pression barométrique n'entrainent des troubles de l'oxygénation. Les contre-indications au voyage aérien sont: les kystes aériques du poumon, les pneumothorax spontanés récidivants, les pneumothorax artificiels à pression élevée, les infections aigues des voies respiratoires supérieures avec exacerbation d'affections pulmonaires chroniques, les affections coronariennes certaines, les insuffisances des cavités droites du coeur, et les hémoptysies récentes.

Editorial

"THEY STUMBLE WHO RUN"

Pulmonary tuberculosis today remains one of our most serious medical, public health and economic problems. In spite of the present generally prevailing optimism we may well heed the recent warning of the English physician Ellman. "In our progressive attitude toward tuberculosis, we should go wisely and slowly. They stumble who run."

Since pulmonary tuberculosis is recognized as being as old or older than civilization its modern treatment can be considered to have begun when Brehmer established the first sanatorium for the treatment of pulmonary tuberculosis just 99 years ago.

The principle of treatment in Brehmer's sanatorium was rest and exercise with the emphasis on prescribed exercise. It was not long until it became evident that the patients who rested most and exercised least obtained the best results and the therapeutic pendulum, at least in the hands of some, swung over to the rest side. Trudeau in 1884 established the first American sanatorium on the principles of rest. Rest as employed by Trudeau, however, was mainly an omission of prescribed exercise, yet he later related that even in advocating that degree of rest he had to bear his share of abuse from his confreres, an experience that, in a sense, has continued to be the lot of the advocates of rest. Today those who have employed rest to its fullest measure believe that the closer the patient with active pulmonary tuberculosis can approach the state of vegetating the more gratifying will be the results.

Pratt very early in this century expressed the opinion that patients with active pulmonary tuberculosis should have "typhoid rest." He was the first to attempt to apply rest through education of patients. He tells of the remarkable cures, including the closure of cavities, by rest alone that he observed in 1917 in reviewing the work of Kinghorn in Saranac Lake. Osler in 1913 taught that, "The treatment of pulmonary tuberculosis was dependent on a rigid regimen, a life of rules and regulations, a dominant will on the part of the doctor and a willing obedience on the part of the patient and friends." Krause in 1918 wrote that, "Until on being asked what is the most important factor in the treatment of pulmonary tuberculosis every patient will unhesitatingly answer rest, a discussion of the subject will always be timely." A modern paraphrase of Krause's statement by Adames is that "Until every *physician* on being asked what is the most important factor in the treatment of pulmonary tuberculosis will unhesitatingly answer rest, a discussion of the subject will always be timely." Bushnell in 1919 emphasized the major importance of the psychological control of the patient and pointed out the striking results possible through this approach. Emerson in 1923 wrote that, "Without rest, all other known measures, important as they may be, will fail." In 1935 he again wrote, "Rest is the only measure in the treatment of pulmonary tuberculosis that has stood the test of time." These statements are just as true today as

they were when they were made by Emerson, with the added emphasis of time. Yet we are all only too familiar with the voluminous literature and many verbal discussions by those in positions of prominence on the treatment of pulmonary tuberculosis or on certain phase of its treatment in which rest is not even mentioned. This circumstance not only contributes to the confusion of the profession but also to the confusion of the patient and those responsible for him. Pinner in 1945 attempted to explain this situation when he wrote that the physician's estimation of the value of rest in the treatment of pulmonary tuberculosis is dependent upon his willingness to try rest over a sufficient length of time to enable him to understand what it will accomplish.

It is to be regretted that in all discussions of the treatment of pulmonary tuberculosis the care of the patient in its entirety is not clearly outlined. It is only by this means that it is possible to determine the value of any of the essentially interdependent therapeutic measures. Logical or scientific deductions obviously cannot be made when only a part is presented as representing the whole.

It is also to be regretted that those interested in research in the treatment of pulmonary tuberculosis yearn only for the laboratory and the test tube and devote little if any attention to the clinical aspects of the disease or to bedside observation and study. The factors which pertain to the employment of rest, however, are variable depending primarily upon the individual so that the results obtained under different circumstances do not readily lend themselves to statistical evaluation. The two basic factors in the application of rest are first, the atmosphere or environment afforded the patient in which to take the cure. This obviously, in different hands, varies from one extreme to the other. The second basic factor is the physician—and physicians are but individuals subject to the same variation in thought, judgment and action as are all other individuals. The advocates of rest are consequently, for the most part, compelled to depend for their convictions upon individual clinical experience.

It must always be understood that rest for the tuberculous patient and rest for the tired healthy person are not synonymous terms. Rest for the tuberculous patient means psychological and physical control and relaxation to the maximum degree possible for each particular patient—a control that is accomplished only through a very close patient-physician relationship which in itself is possible only through a mutual understanding and a mutual confidence. As further pointed out by Pinner, without psychological control, being in bed is not bed rest.

Psychological control of patients may be accomplished through a few simple procedures. The first of which is the treatment of the patient as an individual. The patient is treated as an individual by telling him the truth. It is what is not understood or the uncertainties that upset people in all walks of life. In view of the present justifiable stand that a death or chronic invalidism from pulmonary tuberculosis is, with very few exceptions, due only to somebody's mistake, the truth can always be optimistically presented. It is only when the patient knows the truth that he can face

the situation with complacency, intelligence and efficiency and it must always be remembered that he takes the cure while the physician provides the means. The second step in the psychological control of the patient is placing him in an atmosphere that is conducive to his adjustment to the cure. "The sanatorium should be the patient's school and the physician his teacher." In other words, the treatment of pulmonary tuberculosis is primarily a talking therapy.

While mechanical and antibiotic therapy, at present, are instrumental in saving the lives of a large number of patients and in restoring them to an economic and social efficiency they are not the treatment of pulmonary tuberculosis. Rest and time—prolonged rest in bed—are the treatment of tuberculosis. All other measures regardless of their importance supplement rest and time but they never supplant them.

In the words of Peck, "The use of rest as the basic principle in the treatment of pulmonary tuberculosis admits of no competition with the employment of mechanical, antibiotic or other means of therapy. If at the outset other measures are indicated they can be instituted at the beginning along with rest." It is rare, however, that measures other than the judicious use of antibiotics are indicated at the outset. Since unbelievable results have been obtained in the past by rest alone, with rest enhanced by the judicious use of antibiotic drugs it is entirely possible that even more startling and satisfactory results can be secured. It is only logical, in view of past experience, that patients in general should have an opportunity to find out what they can accomplish by rest or rest plus antibiotics over a reasonable length of time, usually three to six months. A period of strict rest in bed is as a rule beneficial to all patients with active tuberculosis. This is the one procedure that is least likely to be harmful.

The very prominent thoracic surgeon, H. Morriston Davies, in an address to the chest surgeons of London in 1948 said, "The intelligent physician, while wise in his surgery puts his patient to bed, studies the case from all angles, watches his response to a sanatorium regimen, balances the pros and cons before putting up the case for ancillary treatment." As told by Ellman of London, while deploring the rush to ancillary treatment this great surgeon, Morriston Davies, finds his most pleasing success in those patients whom he can send out healed by sanatorium and rest treatment alone.

Edward W. Hayes, M.D.

II International Congress on Diseases of the Chest

The II International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the American College of Chest Physicians, was held in Rio de Janeiro, Brazil, August 28, 29 and 30, 1952. The Congress was held jointly with the XII Congress of the International Union Against Tuberculosis which conducted its sessions on August 25, 26 and 27. The Congresses were endorsed by the Brazilian Government and the Hon. Getulio Vargas, President of Brazil, served as Honorary President. Professor Manoel de Abreu served as President of the Congresses and Dr. Reginaldo Fernandes as Secretary-General. Approximately 1,000 delegates and their wives attended the Congresses, representing many countries throughout the world.

A joint Inaugural Session was held on Sunday evening, August 24, in the auditorium of the Ministry of Education and Health. Dr. Simoes Filho, Minister of Education and Health, represented the Brazilian Government at the Inaugural Session and welcomed the delegates to Rio de Janeiro. Speakers were Professor Manoel de Abreu, Professor Etienne Bernard, France, Secretary-General of the International Union Against Tuberculosis, and Dr. Andrew L. Banyai, U.S.A., President of the American College of Chest Physicians. Musical interludes were presented by members of the Rio de Janeiro Symphony Orchestra.

CONVOCATION AND AWARDING OF COLLEGE MEDAL

A Convocation ceremony, presided over by Dr. Alvis E. Greer, U.S.A., President-Elect, American College of Chest Physicians, was held at the auditorium of the Ministry of Education and Health on Thursday evening, August 28. Dr. Jose Cafe Filho, Vice President of the Republic of Brazil, represented his Government at the Convocation. The highlight of the evening was the awarding of the College Medal to Professor Jorgen Lehmann, Gothenburg, Sweden, for meritorious achievement in the development of para-aminosalicylic acid for the treatment of diseases of the chest. The Medal was presented to Professor Lehmann by Dr. Andrew L. Banyai, President of the American College of Chest Physicians.

Following the presentation of the College Medal, Certificates of Merit were awarded to:

Hon. Getulio Vargas, President, United States of Brazil

Professor Manoel de Abreu, Regent, American College of Chest Physicians and President of the Congresses

Professor Arlindo de Assis, Director of Medicine, Ministry of Education and Health

Professor Affonso Mac Dowell, Honorary Regent, American College of Chest Physicians

Professor Ugo Pinheiro Guimaraes, President, Brazilian Tuberculosis Association

Dr. Reginaldo Fernandes, Governor, American College of Chest Physicians and Secretary-General of the Congresses.

Certificates of Merit were also presented to Past Presidents of the Brazilian Chapters of the American College of Chest Physicians. The Certificates were awarded by Dr. J. Winthrop Peabody, U.S.A., Past President of the College.

Awarding of Fellowship Certificates to new Fellows of the College was made by Dr. Alvis E. Greer and Dr. Donald R. McKay, U.S.A., Chairman of the Board of Regents of the American College of Chest Physicians. Members of the Rio de Janeiro Symphony Orchestra provided musical selections during the program.

INAUGURAL SESSION

II International Congress on Diseases of the Chest

Delegates attending the Inaugural Session of the XII Congress of the International Union Against Tuberculosis and the II International Congress on Diseases of the Chest, Rio de Janeiro, Brazil, August 24, 1952.

EXECUTIVE SESSIONS

Two executive sessions were held during the Congress in Rio de Janeiro which were attended by Regents, Governors and other officials of the American College of Chest Physicians. The opening executive session was held on Saturday, August 23, at the Copacabana Palace Hotel.

Dr. Andrew L. Banyai, President of the College, presided at the executive sessions. At the opening session, Dr. Banyai began the meeting with brief remarks of welcome to the officials present, representing many countries throughout the world. Mr. Murray Kornfeld, Executive Director of the College, gave a brief report of the activities of the Council on International Affairs.

Officials of the College from each country represented, were called upon to present reports of the activities of the College in their respective countries. These reports were received with great interest by the assembly and some discussion followed concerning undergraduate and postgraduate medical education, chapter meetings and programs, and other matters of interest to the group.

The closing executive session was held on Friday, August 29, at the Automobile Club of Rio de Janeiro. The Committee on Nominations presented the following slate of officers to be elected for a period of two years:

HONORARY REGENTS

Brazil: Affonso MacDowell, Rio de Janeiro

Canada: William E. Ogden, Toronto, Ontario

REGENTS

Argentina	Gumersindo Sayago	Cordoba
Australia	W. Cotter Harvey	Sydney
Brazil	Manoel de Abreu	Rio de Janeiro
Canada	Harold I. Kinsey	Toronto
Central America	Amadeo Vicente Mastellari	Panama City
Chile	Hector Orrego Puelma	Santiago
Colombia	Carlos Arboleda Diaz	Bogota
Cuba	Antonio Navarrete	Havana
Ecuador	Juan Tanca Marengo	Guayaquil
France	Etienne Bernard	Paris
Great Britain	Alexander Fleming	London
Greece	Nicholas Oekonomopolous	Athens
India	Raman Viswanathan	New Delhi
Italy	Eugenio Morelli	Rome
Mexico	Donato G. Alarcon	Mexico City
Peru	Ovidio Garcia-Rosell	Lima
Philippine Islands	Miguel Canizares	Manila
Portugal	Lopo de Carvalho	Lisbon
South Africa	David P. Marais	Cape Town
Switzerland	Gustav Maurer	Davos
Uruguay	Fernando D. Gomez	Montevideo
Venezuela	Jose Ignacio Baldo	Caracas

GOVERNORS

Argentina	Raul F. Vaccarezza	Buenos Aires
Australia		
Victoria	Alan H. Penington	Melbourne
New South Wales	G. Bruce White	Sydney
South Australia	Darcy R. W. Cowan	Adelaide
Austria	Erhard F. Kux	Innsbruck
Belgium	Henry Durieu	Brussels

Dr. Andrew L. Banyai, U.S.A., President, American College of Chest Physicians, presenting College Medal to Professor Jorgen Lehmann, Sweden.

GOVERNORS *(Continued)*

Brazil		
Rio de Janeiro	Reginaldo Fernandes	Rio de Janeiro
Minas Gerais	Orlando Cabral Motta	Belo Horizonte
Sao Paulo	Jose Rosemberg	Sao Paulo
Bahia	Jose Silveira	Salvador
Pernambuco	Joaquim Cavalcanti	Recife
Para	Epilogo de Campos	Para
Canada		
Quebec	B. Guy Begin	Montreal
Ontario	Hugo T. Ewart	Hamilton
Eastern Provinces	J. J. Quinlan	Kentville, N. S.
Western Provinces	Leslie Mullen	Calgary, Alberta
Pacific Provinces	W. Elliott Harrison	Vancouver
Ceylon	George E. Ranawake	Colombo
Chile		
Valparaiso	Gilbert O. V. Zamorano	Valparaiso
Santiago	Armando Alonso Vial	Santiago
Concepcion	Ildefonse Garreton Unda	Concepcion
China	Li Shu-Fan	Hong Kong
Colombia	Rafael J. Mejia	Medellin
Costa Rica	Raul Blanco Cervantes	San Jose
Cuba	Teodosio Valledor	Havana
Czechoslovakia	Jaroslav Jedlicka	Prague
Dominican Republic	J. M. Moscoso Cordero	Trujillo
Eastern Pakistan	Mohammed Ibrahim	Dacca
Ecuador	Jorge A. Higgins	Guayaquil
Egypt	Abdel-Aziz Sami	Cairo
El Salvador	Jose Valiente	San Salvador
England		
Greater London	Richard R. Trail	London
Northern England	Peter W. Edwards	Shropshire
Finland	P. E. A. Nylander	Helsinki
France		
Paris	Andre Meyer	Paris
Paris	Maurice Bariety	Paris
Bordeaux	F. Piechaud	Bordeaux
Lyon	Paul Santy	Lyon
Nantes	Paul Veran	Nantes
Germany	Joachim Hein	Schleswig-Holstein
Greece	Basil Papanicolaou	Athens
Guatemala	E. Coronado Iturbide	Guatemala City
Haiti	Louis Roy	Port-au-Prince
India		
Western India	Prag Nath Kapur	Delhi
Northern India	K. L. Wig	Punjab
Eastern India	P. K. Ghosh	Calcutta
Southern India	K. S. Sanjivi	Madras
Ireland	Victor M. Synge	Dublin
Israel	Juda M. Pauzner	Petach-Tikva
Italy		
Southern Italy	Maurizio Ascoli	Palermo
Northern Italy	Attilio Omodei Zorini	Rome
Japan	Jo Ono	Tokyo
Korea	In Sung Kwak	Seoul
Lebanon	Papken S. Mugrditchian	Beirut

Some of the Regents of the American College of Chest Physicians attending the Convocation held in Rio de Janeiro, August 27, 1952. Standing, left to right: Drs. Jorgen Lehmann, William A. Hudson, J. Winthrop Peabody, Donald R. McKay, Edward Greco, Louis Mark, Alvis E. Greer, Andrew L. Banyai, Richard H. Overholt, James H. Stygall (background), Murray Kornfeld, John F. Briggs, Reginaldo Fernandes and J. Arthur Myers.

GOVERNORS *(Continued)*

Mexico	Miguel Jimenez	Mexico City
Netherlands	Ite Boerema	Amsterdam
Nicaragua	Rene Vargas	Managua
Norway	Carl B. Semb	Oslo
Panama	Augustin A. Sosa	Panama City
Paraguay	Angel R. Gines	Asuncion
Peru	Max Espinoza Galarza	Lima
Philippine Islands	Manuel Quisumbing, Sr.	San Pablo
Portugal	Carlos Alberto Vidal	Lisbon
Scotland	Robert Y. Keers	Aberdeenshire
South Africa		
Southern States	Theodore Schrire	Cape Town
Northern States	Maurice A. Pringle	Transvaal
Spain	Antonio Crespo Alvarez	Madrid
Sweden	Erik Hedvall	Uppsala
Switzerland	Maurice Gilbert	Geneva
Turkey	Tevfik Saglam	Istanbul
Uruguay	Armando Sarno	Montevideo
Venezuela	Julio Criollo Rivas	Caracas
Yugoslavia	Robert T. Neubauer	Golnik

The slate of officers as presented by the Committee on Nominations, upon motion from the floor, was duly elected.

Invitations to hold the III International Congress on Diseases of the Chest were received from the following countries: Canada, Spain, Switzerland, Turkey and the U.S.A. The invitations were referred to the Executive Council and after due consideration the invitation to hold the III International Congress on Diseases of the Chest in Barcelona, Spain was accepted.

The following resolutions were presented and adopted:

WHEREAS In accord with the College By-Laws, all candidates for Fellowship in the American College of Chest Physicians are obliged to pass an oral and written examination; the purpose of this provision is to elevate the standards for physicians who wish to practice in the specialty of diseases of the chest; this ruling has been effective in the United States of America since 1944 and in Canada since 1950.

BE IT THEREFORE RESOLVED That effective January 1, 1953, all candidates for Fellowship in the American College of Chest Physicians be required to pass oral and written examinations. The examinations are to be prepared by the Board of Examiners and sent to the Regents and Governors of the American College of Chest Physicians in the respective countries for translation. The Regents and Governors are to arrange for the examination of all candidates for Fellowship in the College at a time and place most convenient to all concerned. Fellowship certificates will be awarded to those candidates who have successfully passed their examinations and will be presented to them at the International Congresses and at other meetings of the College, as directed by the Board of Regents.

The Council on International Affairs of the American College of Chest Physicians desires to express its appreciation to the International Union Against Tuberculosis for the fine cooperation which has been given by the Union to the II International Congress on Diseases of the Chest. This cooperation has made it possible to hold two successful congresses in the City of Rio de Janeiro. Both organizations are of the opinion that in organizing future congresses, a close cooperation should exist between the International Union Against Tuberculosis and the Council on International Affairs of the American College of Chest Physicians. It is proposed that the officials of both organizations consult together in the selection of cities and dates before a final decision is made. This close cooperation will enable members of both organizations to

OPENING EXECUTIVE SESSION

II International Congress on Diseases of the Chest

Some of the officials in attendance at the Opening Executive Session, Copacabana Palace Hotel, Rio de Janeiro, Brazil, August 23, 1952.

attend the two congresses without inconvenience and loss of time in traveling between cities where the congresses are to be held, as well as a saving of expenses involved in such travel.

WHEREAS The officials of the Government of the United States of Brazil and the officials of the Congress have been most cordial in their reception of members of the American College of Chest Physicians, and

WHEREAS Their warm hospitality has exceeded all expectations,

BE IT RESOLVED That the American College of Chest Physicians extend their thanks and appreciation to the Hon. Getulio Vargas, President of the Republic of Brazil, Professor Manoel de Abreu, President of the Congress and President of the Central Brazilian Chapter of the College, Dr. Reginaldo Fernandes, Secretary-General of the Congress and Governor of the Central Brazilian Chapter of the College, Professor Affonso Mac Dowell, Regent of the College for Brazil, and to all of our other officers and members in Brazil.

BE IT FURTHER RESOLVED That thanks be given to Mrs. Manoel de Abreu and her committee of ladies for the organization of a wonderful reception and entertainment for the ladies who have come to Brazil from many countries.

BE IT FURTHER RESOLVED That appreciation be expressed to all of the secretaries and workers in the administrative offices of the Congress for their efforts in helping to make the Congress a success.

BE IT FURTHER RESOLVED That a special vote of thanks and appreciation be extended to the members of the press and to the photographers who have cooperated so effectively in publicizing this II International Congress on Diseases of the Chest.

SCIENTIFIC PROGRAM

During the three days of the scientific program presented by the Council on International Affairs of the American College of Chest Physicians, 86 papers were presented in the four official languages of the Congress, namely, Portuguese, Spanish, French and English. One morning of the scientific session was devoted to a joint program with the International Bronchoesophagological Society.

MOTION PICTURES

Simultaneously with the scientific sessions, 22 motion pictures dealing with various aspects of diseases of the chest were presented in an adjacent assembly room. The complete program of motion pictures was repeated on each day during the scientific sessions.

The II International Congress on Diseases of the Chest closed on Saturday, August 30. The three days of scientific presentations and motion pictures were well attended. During the week sight-seeing tours and luncheons were attended by the ladies, which had been arranged by Mrs. Manoel de Abreu and the members of her committee. Receptions were given during the week by the Embassies of various countries, among which was a delightful reception by Mr. Herschel Johnson, American Ambassador to Brazil.

The Congress was climaxed by a banquet and grand ball on Saturday night, August 30, which was given at the Copacabana Palace Hotel.

On Monday, September 1, the delegates were the guests of the Government of Sao Paulo, Brazil. Airplanes were provided to fly the physicians and their wives to Sao Paulo in the morning where busses met them at the airport and took them for a tour of the city, including a visit to the famous Butantan Snake Institute and the University of Sao Paulo. A luncheon was given for the delegates at the Hotel Esplanade which was presided over by Dr. Jose Rosemberg, the Governor of the College for Sao Paulo, and the address of welcome was made by the Secretary of Public Health of Sao Paulo. Dr. Andrew L. Banyai, the President of the College, responded. A brief talk was also given by Dr. Raul Soules-Baldo, a Fellow of the College, Minister of Health for Venezuela. The visit of the delegates to Sao Paulo was made possible through the courtesy of Dr. Lucas Nogueira Garcez, Governor of the State of Sao Paulo, Brazil.

BANQUET AND GRAND BALL
II International Congress on Diseases of the Chest
XII Congress, International Union Against Tuberculosis

HONORARY COMMITTEE

Brazilian Officials

Hon. Getulio Vargas
President of Brazil

Dr. Jose Cafe Filho
Vice President of Brazil

Dr. Joao Neves da Fontoura
Minister of the Exterior

Dr. Simoes Filho
Minister of Education and Health

Dr. Negrao de Lima, Minister
of Justice and Interior Relations

Dr. Segadas Vianna, Minister
of Labor, Industry and Commerce

Dr. Horacio Lafer
Minister of Finance

Dr. A. Souza Lima, Minister
of Transport and Public Works

General Cyro do Espirity Santo
Cardoso, Minister of War

Admiral Renato Guilhobel
Minister of the Navy

Dr. Joao Cleophas
Minister of Agriculture

Brigadier Nero Moura
Minister of Aviation

Dr. Joao Carlos Vital
Mayor of the Federal District of Brazil

Dr. Lucas Nogueira Garcez
Governor of Sao Paulo, Brazil

Ambassadors

Argentina, Dr. Juan I. Cooke
Belgium, Mr. Marcel Henry Jasper
Bolivia, Mr. Alberto Virreira
Canada, Dr. Ephraim Herbert Coleman
Chile, Mr. Oswaldo Vidal
China, Mr. Shen Chin-Ting
Colombia, Dr. Dario Botero Isaza
Cuba, Mr. Gabriel Landa
Dominican Republic, Dr. Vidor Garrido
Ecuador, Mr. Arturo Barrero
Egypt, Dr. Jusein Chauky Bey
France, Mr. Gilbert Arvengas
Germany, Dr. Fritz Oellers
Great Britain, Mr. Geoffrey Harrington
Spain, Mr. Pedro de Prat y Soutzo
Turkey, Mr. Fuad Carin
U.S.A., Mr. Herschel V. Johnson
Uruguay, Dr. Giordano B. Eccher
Venezuela, Dr. Tito Gutierrez Alfaro

Ministers

Australia, Mr. Peter Richard Heyden
Austria, Mr. Adrian Rotter
Costa Rica,
Mr. Edmond Gerlei de Pauliny
Czechoslovakia, Dr. Jan Cech
Denmark, Mr. Otto Wadstad
Finland, Mr. T. O. Bahervnori
Greece, Mr. Paul Economon-Gouvas
Guatemala,
Dr. Jose Luis Aguillar de Ison
Haiti, Mr. Pierre Rigand
India, Mr. Minocheler Rustow Masani
Italy, Dr. Mario Augusto Martin
Iran, Mr. Hasanali Gaffery
Israel, General David Shaltiel
Mexico, Dr. Antonio Villalobos
Nicaragua,
Mr. Justino Lanson Balladores
Norway, Mr. Herik Andreas Brock
Panama, Mr. Jose Ignacio Queiros
Paraguay, Dr. Fabio da Silva
Peru, Dr. Felipe Tudella
Poland, Prof. Wojeieck Wzosek
Syria, Mr. Omar Abou-Richer
Sweden, Mr. Knut Richard Thyberg
Switzerland, Dr. Eduard A. Feer
Yugoslavia, Dr. Rajko Djermanovic

URUGUAY CHAPTER

On Thursday, September 4, a group of delegates that had attended the II International Congress on Diseases of the Chest in Rio de Janeiro arrived in Montevideo to meet with the members of the Uruguay Chapter of the College. Due to a delay in Rio de Janeiro, the group did not reach Montevideo on the day originally scheduled and thereby missed the scientific session planned by the Chapter for Wednesday, September 3, as well as the reception of the Hon. Edward L. Roddan, American Ambassador, which was held at the American Embassy on Wednesday evening. Dr. Fernando D. Gomez, Regent of the College for Uruguay, arranged a

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dinner meeting for the delegation and the Uruguay members, which was held at the Parque Hotel on Thursday evening, September 4. Dr. Gomez gave a brief address of welcome and officials of the College from Uruguay and other countries were introduced. The following day was spent in a sight-seeing tour of Montevideo and the delegation then left for Buenos Aires.

ARGENTINE CHAPTER

On Friday, September 5, the delegation arrived in Buenos Aires, Argentina, and attended a luncheon meeting sponsored by the Argentine Chapter of the College. That evening a scientific session was presented at the Association Medica Argentina, sponsored by the chapter. Dr. T. Villafane Lastra, President of the Argentine Chapter, presided at the meeting. The Regent of the College for Argentina, Dr. Gumersindo Sayago, and the Governor, Dr. Raul F. Vaccarezza, participated in the program.

The delegation attended sessions of the Fourth Inter-American Cardiological Congress on Saturday, September 6, and also visited clinics and tuberculosis institutes in Buenos Aires. In the evening, a "Folklore" party was given for the delegates by Drs. Raul Vaccarezza, Alberto Soubrie and Acevado Cucchiani at their private club.

The Inaugural Session of the First Argentine Congress on Thoracic Surgery took place on Monday, September 8, and was attended by the delegates and the members of the Argentine Chapter of the College. On Monday evening the American Ambassador, Hon. Albert F. Nufer, gave a reception at the American Embassy residence. The following morning the delegates departed from Buenos Aires and flew across the Andes to Santiago, Chile.

CHILEAN CHAPTER

The Chilean Chapter of the College welcomed the delegates to Santiago on Tuesday, September 9. On Tuesday evening, the Chilean-North American Cultural Institute gave a reception for the College members.

A scientific session sponsored by the Chilean Chapter of the College, the Medical Society of Santiago and the Chilean Tuberculosis Society was presented on Wednesday, September 10, at the Central Auditorium of the Hospital del Salvador and Dr. Armando Alonso Vial, Governor of the College for Santiago, was introduced. Dr. Alonso Vial was host at a luncheon in honor of the thoracic surgeons given at the country club.

A reception was given by the Institute of Inter-American Affairs of the U. S. Department of State on Wednesday evening at the Hotel Carrera. Dr. Theodore Gandy, Director of the Institute of Inter-American Affairs in Chile, was the host. The delegates had the opportunity of meeting the American Ambassador, Hon. Claude Bowers, who attended the reception.

On Thursday morning the delegates visited the Trudeau Sanatorium where a reception was given for them, and in the evening, a scientific session was presented at the Auditorium of the Clinica Santa Maria, sponsored by the Chilean Chapter of the College and the Chilean Tuberculosis Society. The delegates left Santiago for Lima, Peru early Friday afternoon.

PERUVIAN CHAPTER

The Peruvian Chapter of the College sponsored a scientific session on Saturday morning, September 13, which was held at the Central Anti-Tuberculosis Dispensary. Dr. Ovidio Garcia Rosell, Regent of the College for Peru, presided at the meeting and introduced Dr. Max Espinoza Galarza, Governor of the College, and Dr. Luis Escudero Villar, President of the Peruvian Chapter. Dr. Leopoldo Molinari was inducted as President of the Peruvian Chapter at the meeting. Dr. Mario Pastor, President of the Peruvian Tuberculosis Association was introduced and gave a brief address. The scientific presentations followed. At the end of the

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scientific program a reception was given at the hospital for the delegates. Luncheon was served to the delegates at the Hospital-Sanatorium No. 1, Bravo Chico, and a tour of the hospital was made in the afternoon.

On Saturday evening, Dr. Ovidio Garcia Rosell and his mother gave a delightful reception at their home for the delegates and the members of the Peruvian Chapter.

The delegates made a tour of Lima on Sunday morning and visited the Presidential Palace and the Archeological Museum. Dr. and Mrs. Molinari received the delegates at the hacienda at Nana, in the Chosica Valley, where a "Pachamanca," or barbecue luncheon, was served.

The Mayor of Lima received the delegates at noon on Monday and the American Ambassador, Hon. Harold H. Tittmann, gave a reception at the Embassy residence that afternoon. The delegates departed for Panama on Monday evening.

CENTRAL AMERICAN CHAPTER

The delegates arrived in Panama City early Tuesday morning, September 16, and spent the day touring the city and visiting the locks of the Panama Canal. At 5 p. m. the American Ambassador, Hon. John C. Wiley, received the delegates and members of the College in Panama at the Embassy residence. That evening a scientific session was presented at the Gorgas Memorial Institute, sponsored by the Central American Chapter of the College, with the cooperation of the National Medical Association, the Isthmian Medical Association and the Academia Panamena de Medicina y Cirugia. In the absence of Dr. Amadeo V. Mastellari, Regent of the College for Central America, Dr. Augustin A. Sosa, Governor, and Dr. Maximo Carrizo, President of the Chapter, conducted the meeting. Early the following morning the delegates departed for their flight back to the United States.

FLYING CONGRESS

Fifty-eight physicians and their wives attending the II International Congress on Diseases of the Chest in Rio de Janeiro, Brazil, left New York City on August 21, 1952, in a group aboard Pan American World Airways Stratocruiser "El Presidente." Dr. William J. Branday, Medical Director of the tuberculosis sanatorium in Trinidad, and a Fellow of the College, joined the flight at Trinidad, B. W. I.

During the nineteen hours of flight, scientific material and entertainment features were presented. The program consisted of the presentation of "The Problem of Selecting Pulmonary and Cardiac Patients for Transportation by Airplane" by Dr. Burgess L. Gordon, Philadelphia, which appears in this issue, several medical and surgical motion picture films, and entertainment films including cartoons and travelogues. This was an historic event, being the first time that a scientific program had been given 18,000 feet in the air.

CERTIFICATES AWARDED TO MURRAY KORNFELD

The Executive Director of the American College of Chest Physicians, Mr. Murray Kornfeld, was presented with certificates of merit in commemoration of twenty-five years of service devoted to the educational advancement in the specialty of diseases of the chest. The certificates were awarded to Mr. Kornfeld by the chapters of the College in Uruguay, Argentina, Chile, Peru, Panama and Mexico. The Brazilian and Mexican Tuberculosis Societies presented Mr. Kornfeld with certificates of Honorary Membership. On November 7, Mr. Kornfeld was awarded a certificate of merit at a meeting of the Cuban Chapter held at the Curie Hospital, Havana, in recognition of twenty-five years of service.

College Chapter News

QUEBEC CHAPTER ORGANIZED

Officials of the College being greeted at Montreal airport upon arrival to attend the organizational meeting of the Quebec Chapter. Standing, left to right: Dr. J. J. Laurier; Dr. Fernand Hebert; Dr. Andrew L. Banyai, President; Dr. Francis M. Woods; Mr. Murray Kornfeld; and Dr. B. Guy Begin.

The first Canadian Chapter of the College was organized in Quebec on October 24, 1952. The meeting was held at the Sacre-Coeur Hospital in Montreal where a scientific program was presented in the morning, presided over by Dr. Fernand Hebert, medical director of the hospital. The members were guests of the hospital at a luncheon. Officers elected for the Quebec Chapter are:

Fernand Hebert, Montreal, President
George R. Howell, Montreal, First Vice President
George Gregoire, Quebec, Second Vice President
J. J. Laurier, Montreal, Secretary
Malcolm A. Hickey, Ste. Agathe des Monts, Treasurer.

Guest speakers were Dr. Andrew L. Banyai, Milwaukee, Wisconsin, President of the College, and Dr. Francis M. Woods, Brookline, Governor of the College for Massachusetts. Dr. B. Guy Begin, Montreal, Governor of the College for Quebec, was in charge of arrangements for the organizational meeting of the new chapter.

NEW YORK STATE CHAPTER

The New York State Chapter will hold its Annual Clinical Meeting at the Hotel New Yorker, New York City on February 19, 1953.

The 13th Annual Meeting of the New York Chapter will be held at the Hotel Statler, Buffalo on May 7, 1953. Dr. William A. Hudson, 1st Vice-President of the College, Detroit, Michigan, has been selected to give the 3rd Annual Howard Lilienthal Lecture.

COLLEGE EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

19th Annual Meeting, American College of Chest Physicians, Hotel New Yorker, New York City, May 28-31, 1953.

Interim Session, Semi-Annual Meeting, Board of Regents, St. Louis, Missouri, November 29-30, 1953.

20th Annual Meeting, American College of Chest Physicians, San Francisco, California, June 17-20, 1954.

3rd International Congress on Diseases of the Chest, Barcelona, Spain, Fall of 1954.

POSTGRADUATE COURSES

Los Angeles Chest Disease Symposium, January 22-23, 1953.

Postgraduate Course, Diseases of the Chest for General Practitioners, Milwaukee, Wisconsin, March 4, 11, 18, 25, 1953.

6th Annual Postgraduate Course on Diseases of the Chest, Philadelphia, Pennsylvania, March 23-27, 1953.

8th Annual Postgraduate Course on Diseases of the Chest, Chicago, Illinois, September, 1953.

6th Annual Postgraduate Course on Diseases of the Chest, Hotel New Yorker, New York City, November 2-6, 1953.

CHAPTER MEETINGS

Annual Clinical Session, New York State Chapter, Hotel New Yorker, New York City, February 19, 1953.

Potomac Chapter Meeting, White Sulphur Springs, West Virginia, April 10, 1953.

Florida Chapter Meeting, Hollywood, Florida, April 26, 1953.

13th Annual Meeting, New York State Chapter, Hotel Statler, Buffalo, New York, May 7, 1953.

MEDICAL SERVICE BUREAU

POSITION WANTED

Male tuberculosis specialist seeks position with institution; age 38; experienced in collapse therapy, thoracoscopy, bronchoscopy, radiology, and BCG; Canadian citizen. Please address all inquiries to Box 268B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Clinical Director wanted for 750 bed Tuberculosis Hospital in Southwest. Starting salary $7,500, then to $9,000 with complete maintenance. Must be citizen of U.S. and an American graduate. Address Box 258A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Staff physician wanted, 180 bed Tuberculosis Hospital. American or Canadian graduate, eligible for Michigan license. Salary $7,500 to $10,000 depending on qualifications and experience. Address Box 259A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Staff physician wanted for 185 bed Tuberculosis Sanatorium located in North Alabama. Position is Assistant to Medical Director. Must be specialist in tuberculosis or internal medicine. Work covers all aspects of medical and surgical treatment. Salary open. Address Box 260A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Assistant Medical Director wanted for 200 bed Tuberculosis Hospital, approved by American College of Surgeons. Applicant must have experience in tuberculosis field and be eligible for Michigan license. Excellent salary and generous fringe benefits offered. Please address Box 261A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Staff physician, Minnesota State Sanatorium, Ah-gwah-ching, Minnesota; preferably under 50, either sex. Salary $8,088 to $9,048. Tuberculosis experience desirable, not required. Full maintenance, single or married. Life in Northern Minnesota's vacation land!

Staff or Resident physician by fully approved tuberculosis hospital with complete facilities. Salary open. Single or family maintenance. Graduate of American University only. Apply Healthwin Hospital, South Bend, Indiana.

POSTGRADUATE COURSE IN BRONCHO-ESOPHAGOLOGY AND PERORAL ENDOSCOPY

The next course in Broncho-esophagology and Peroral Endoscopy will take place at the Temple University School of Medicine, 3400 N. Broad Street, Philadelphia, February 23rd to March 6th, 1953, and the fee is $250. Further data concerning the course and application blanks will be sent on request.

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